



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> : A61K 31/58, 45/06 // (A61K 31/58 A61K 31:44)	A1	(11) International Publication Number: WO 92/18132 (43) International Publication Date: 29 October 1992 (29.10.92)
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(21) International Application Number: PCT/US92/02749

(22) International Filing Date: 6 April 1992 (06.04.92)

## (30) Priority data:

686,720	17 April 1991 (17.04.91)	US
746,388	16 August 1991 (16.08.91)	US
846,155	11 March 1992 (11.03.92)	US

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(81) Designated States: AT (European patent), AU, BB, BE (European patent), BF (OAPI patent), BG, BJ (OAPI patent), BR, CA, CF (OAPI patent), CG (OAPI patent), CH (European patent), CI (OAPI patent), CM (OAPI patent), CS, DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GA (OAPI patent), GB (European patent), GN (OAPI patent), GR (European patent), HU, IT (European patent), JP, KR, LK, LU (European patent), MC (European patent), MG, ML (OAPI patent), MN, MR (OAPI patent), MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent).

**Published***With international search report.**Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.*

(54) Title: PHARMACEUTICAL COMBINATION FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA CONTAINING A 5 ALPHA-REDUCTASE INHIBITOR

## (57) Abstract

Disclosed is a new treatment for men with benign prostatic hyperplasia (BPH), involving combination therapy of a 5 $\alpha$ -reductase inhibitor, e.g. a 17 $\beta$ -substituted non-azasteroid, 17 $\beta$ -acyl-3-carboxy-androst-3,5-diene, benzoylaminophenoxybutanoic acid derivative, fused benz(thio)amide or cinnamoylamide derivative, aromatic 1,2-diethers or thioethers, aromatic ortho acylaminophenoxy alkanolic acids, ortho thioalkylacylamino-phenoxy alkanolic acids, pharmaceutically acceptable salts and esters thereof, e.g. finsteride, in combination with an aromatase inhibitor, i.e., fadrazole, being 4-(5,6,7,8-tetra-hydroimidazo-[1,5- $\alpha$ ]pyridin-5-yl)benzonitrile. The combination provides therapy at the molecular level for the underlying cause of the disease as well as providing symptomatic relief. Pharmaceutical compositions useful for treatment are also disclosed.

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10 TITLE OF THE INVENTION

PHARMACEUTICAL COMBINATION FOR THE TREATMENT OF BENIGN PROSTATIC HYPERPLASIA  
CONTAINING A 5 ALPHA-REDUCTASE INHIBITOR

CROSS REFERENCE TO RELATED APPLICATIONS

15 This application is a Continuation- in-Part  
of U.S. Application Serial No. 07/746,388, (Case  
18364IA) filed August 16, 1991, which in turn is a  
continuation-in-part application of U.S.S.N.  
07/686,720, (Case 18364) filed on April 17, 1991.

20

BACKGROUND OF THE INVENTION1. Field of the Invention

25 This invention relates to a new method of  
treatment for patients, i.e. men having benign  
prostatic hyperplasia (BPH), involving combination  
therapy of administering therapeutically effective  
amounts of a 5 $\alpha$ -reductase inhibitor in combination  
30 with an aromatase inhibitor.

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## 2. Background of the Invention

Benign prostatic hyperplasia (BPH) affects a substantial number of males over the age of 50 and usually requires surgery in advanced stages for relief.

It is known that testosterone (T) is secreted by the testes and adrenal glands but can undergo a  $5\alpha$ -reductase mediated conversion to dihydrotestosterone (DHT) in peripheral sites including the liver, skin, and prostate. DHT is preferentially bound by the nucleus of prostatic cells thus indicating that DHT, rather than T, is the primary androgen required by the prostate for its growth and function. This led to the hypothesis that, by inhibiting  $5\alpha$ -reductase, the formation of DHT could be curtailed and hopefully prostate regression obtained.

Finasteride, 17 $\beta$ -(N-t-butyl)carbamoyl-4-aza- $5\alpha$ -androst-1-en-3-one, was developed as a compound which was found to inhibit  $5\alpha$ -reductase and exhibit positive effects against benign prostatic hyperplasia. Finasteride is a 4-azasteroid and a competitive inhibitor of the enzyme. It shows no affinity for the androgen receptor and so would not be expected to interfere with the binding and action of T in those tissues, such as muscle, which respond to T, and thus should not result in feminizing characteristics.



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Typical 4-aza steroid 5 $\alpha$ -reductase inhibitors known in the art include those developed by Merck. (See U.S. Pat. 4,377,584 to Rasmusson, et al.; U.S. Pat. 4,220,735 to Rasmusson, et al.; U.S. Pat. 4,845,104 to Carlin, et al.; U.S. Pat. 4,760,071 to Rasmusson, et al., which discloses finasteride, being 17 $\beta$ -(N-t-butyl)carbamoyl-4-aza-5 $\alpha$ -androst-1-en-3-one, known by its trademark as PROSCAR<sup>®</sup>; U.S. Pat. 4,732,897 to Cainelli, et al.; U.S. Pat. 4,859,681 to Rasmusson, et al.; EPO Publn. 0 155 076; EPO Publn. 0 004 949; and EPO Publn. 0 314 189.

It is also known that small amounts of estrogens, i.g. estradiol, may be formed in the testes and prostate by the action of the enzyme, aromatase. It is not clear exactly how these formed estrogens participate biochemically, but they are implicated and associated with prostate enlargement, i.e. benign prostatic hyperplasia.

USP 4,598,072 to Schering AG describes the combination of an aromatase inhibitor and an anti-androgen for treatment of benign prostatic hyperplasia. However, specific 5-alpha reductase inhibitors are not suggested or mentioned as suitable anti-androgen agents.

What is desired in the art is a combination therapy both to treat the underlying DET-dependent cause of BPH and to treat the estrogen-dependent associated cause of the disease as well.

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SUMMARY OF THE INVENTION

By this invention there is provided a method of treating patients with benign prostatic hyperplasia who are in need of such treatment comprising the step of administering in combination to such patients therapeutically effective amounts of a  $5\alpha$ -reductase inhibitor, e.g. a  $17\beta$ -substituted non-azasteroid,  $17\beta$ -acyl-3-carboxyandrost-3,5-diene, benzoylamino-phenoxybutanoic acid derivative, fused benz(thio)-amide or cinnamoylamide derivative, aromatic 1,2-diethers or thioethers, aromatic ortho acylamino-phenoxy alkanolic acids, ortho thioalkylacylamino-phenoxy alkanolic acids, pharmaceutically acceptable salts and esters thereof, and an aromatase inhibitor.

The combined effect of a  $5\alpha$ -reductase inhibitor in inhibiting DHT production in the prostate and the aromatase inhibitor, i.e. fadrazole, will result in a greater effect on suppressing the growth and symptomatic relief of enlarged prostate than either agent by itself.

BRIEF DESCRIPTION OF THE  
INVENTION AND PREFERRED EMBODIMENTS

In one preferred aspect, the present invention provides an effective method of treating BPH in patients in need of symptomatic relief by administering therapeutically effective amounts of the aromatase inhibitor in association with a

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5 $\alpha$ -reductase inhibitor or pharmaceutical composition thereof. The active compounds may be administered together or in any order, as discussed hereinafter.

5 By the term "patients in need of such treating" is meant male patients with functioning gonads who are being treated with a 5 $\alpha$ -reductase inhibitor in a therapeutic program designed to combat benign  
10 prostatic hyperplasia (BPH) and are discovered to be in need of symptomatic relief.

The use of therapeutically effective amounts of the 5 $\alpha$ -reductase inhibitor and the aromatase  
15 inhibitor in accordance with this invention effectively treats the adverse symptoms of BPH including nocturia, hesitancy, decreased urinary flow, and the like.

Aromatase is an enzyme complex incorporating  
20 ing a NADPH-cytochrome c-reductase and a cytochrome P<sub>450</sub> component which mediates the conversion of androgens to estrogens, Bellino, J. Steroid Biochem. 17:261-270 (1982). The reaction is believed to involve three hydroxylation steps, two at the C-19  
25 position (Meyer, Biochem. Biophys. Acta 17: 441-442 [1955]; Marato et al., Biochem. Biophys. Res. Comm. 6: 334-338 [1961]) and one at C-2 (Hahn and Fishman, J. Biol. Chem. 259: 1689-1694 [1984]; Brodie et al., J. Am. Chem. Soc. 91: 1241-1242 [1969]) which result  
30 in the conversion of the A ring of the androgen molecule to an aromatic ring. Since aromatization is a unique reaction in the biosynthesis of steroids, specific inhibitors should not cause deprivation of other

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essential steroids. The inhibition or blocking of the conversion of androgens (testosterone, androstenedione) to estrogens (estradiol, estrone) results in an accumulation of androgens (testosterone, androstenedione) which may be responsible for participating in or mediating benign prostatic hyperplasia.

An aromatase inhibitor as defined herein is any steroidal or non-steroidal compound which prevents the conversion of androgens to estrogens. The compounds include substrate analogues of androstenedione, testosterone or other steroidal substances involved in the aromatase pathway, Henderson, J. Steroid Biochem. 27: 905-914 (1987).

Non-steroidal compounds that block aromatase activity are also included within the scope of the invention. These non-steroidal compounds include compounds or analogues that can bind to the enzymatic active site of aromatase and inhibit enzymatic activity. Non-steroidal or steroidal compounds will also include compounds or analogues that bind to the enzyme at a site away from the enzymatic site and cause a structural change in the enzyme which results in a loss of enzymatic activity. Aromatase inhibitors further include non-steroidal compounds that interfere with cytochrome P<sub>450</sub> mediated hydroxylations such as those described by Brodie, et al., J. Steroid Biochem. 27: 899-903 (1987).

The following compounds are known non-steroidal aromatase inhibitors as disclosed by the associated reference. The reference will also directly contain a method for making the compound

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or will direct one who wishes to use the compound to a method for producing the compound. The aromatase inhibitors of the instant invention known in the art include, but are not limited to, the following compounds:

- 5 [(1H-imidazol-1-yl)phenylmethyl]-1-methyl-1H-benzotriazole, 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole as described in EPO Publication No. 293,978, and USP 4,943,574;
- 10 2,2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]-di(2-methylpropiononitrile), 2,2-[5-(imidazol-1-ylmethyl)-1,3-phenylene]-di(2-methylpropiononitrile), 2-[3-(1-hydroxy-1-methylethyl)-5-(1H-1,2,4-triazol-1-ylmethylphenyl)]-2-methylpropiononitrile, 2,2-[5-dideu-
- 15 terio-(1H-1,2,4-triazol-1-yl)methyl-1,3-phenylene]di-(2-trideuteriomethyl-3,3,3-(trideuterio-propiononitrile), and 2,2-[5-dideuterio(1H-1,2,4-triazol-1-ylmethyl-1,3-phenylene)di(2-methyl-propiononitrile) as disclosed in European Patent Application,
- 20 Publication No. 296,749; 1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]furanone, 1,2,-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho-[2,1-b]-furan-7-carbonitrile, 1,2-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-
- 25 1-ylmethyl)-naphtho[2,1-b]furan-7-carboxamide, and 1,2-dihydro-1,1-dimethyl-2-oxo-8-[di(1H-1,2,4-triazol-1-yl)methyl]naphtho[2,1-b]furan-7-carbo-
- nitrile as disclosed in European Patent Application, Publication No. 316,097;

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2-(4-chlorobenzyl)-2-fluoro-1,3-di(1,2,4-triazol-1-yl)  
propane, 2-fluoro-2-(2-fluoro-4-chlorobenzyl)-1,3-di  
(1,2,4-triazol-1-yl)propane, 2-fluoro-2-(2-fluoro-4-  
trifluoromethylbenzyl)-1,3-di(1,2,4-triazol-1-yl)-  
5 propane, 3-(4-chlorophenyl)-1-(1,2,4-triazol-1-yl)-  
2-(1,2,4-triazol-1-ylmethyl)butan-2-ol, 2-(4-chloro-  
- $\alpha$ -fluorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propan-  
2-ol, 2-(4-chlorobenzyl)-1,3-bis(1,2,4-triazol-1-yl)-  
propane, 4-[2-(4-chlorophenyl)-1,3-di(1,2,4-triazol-  
10 1-ylmethyl)ethoxymethyl]-benzonitrile, 1-(4-fluoro-  
benzyl)-2-(2-fluoro-4-trifluoromethylphenyl)-1,3-di-  
(1,2,4-triazol-1-yl)propan-2-ol, 2-(4-chlorophenyl)-  
1-(4-fluorophenoxy)-1,3-di(1,2,4-triazol-1-yl)propan-  
2-ol, 1-(4-cyanobenzyl)-2-(2,4-difluorophenyl)-1,3-di-  
15 (1,2,4-triazol-1-yl)-propan-2-ol and 2-(4-chloro-  
phenyl)-1-phenyl-1,3-di(1,2,4-triazol-1-yl)-propan-  
2-ol as described in European Patent Application,  
Publication No. 299,684; 5-bis(4-chlorophenyl)  
methylpyrimidine as disclosed in U.S. Patent  
20 No. 4,762,836;  $\alpha,\alpha$ -bis(4-chlorophenyl)-2-  
pyrazinemethanol as described in U.S. Patent No.  
4,764,376; N-(2,4-difluorophenyl)-N-benzyl-3-  
pyridinemethanamine and N-(2-chlorophenyl)- $\alpha$ -  
(4-fluorophenyl)-3-pyridinemethanamine as disclosed  
25 in U.S. Patent No. 4,744,251; 1-(10,11-dihydro-4H-  
dibenzo[a,d]cyclohepten-4-yl)-1H-imidazole and  
1-(9H-fluoren-9-yl)-1H-imidazole as disclosed in  
U.S. Patent No. 4,757,082; 3-bis(4-chlorophenyl)-  
3-methylpyridine and  $\alpha,\alpha$ -bis(4-chlorophenyl)-  
30 3-pyridinemethanol as disclosed in U.S. Patent No.  
4,757,076; 5H-5-(4-cyanophenyl)-6,7-dihydropyrrolo  
[1,2-c]imidazole and 5H-5-(4-cyanophenyl)-6,7,8,9-

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tetrahydroimidazo[1,5-a]azepine and disclosed in U.S. Patent No. 4,728,645; 5-[(1H-imidazol-1-yl)phenylmethyl]-2-methyl-1H-benz-imidazole and 5-[(3-chlorophenyl)(1H-imidazol-1-yl)-methyl-1H-benzimidazole as disclosed in European Patent Application, Publication No. 260,744; (Z)- $\alpha$ -(1, 2, 4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile, (Z)-4'-chloro- $\alpha$ -(1,2,4-triazol-1-ylmethyl)stilbene-4-carbonitrile, (Z)- $\alpha$ -1,2,4-triazol-1-ylmethyl)-4'-(trifluoromethyl)stilbene-4-carbonitrile, (E)- $\beta$ -fluoro- $\alpha$ -(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile, (Z)-4'-fluoro- $\alpha$ -(imidazol-1-ylmethyl)stilbene-4-carbonitrile, (Z)-2',4'-dichloro- $\alpha$ -(imidazol-1-ylmethyl)-stilbene-4-carbonitrile, (Z)-4'-chloro- $\alpha$ -(imidazol-1-ylmethyl)stilbene-4-carbonitrile, (Z)- $\alpha$ -(imidazol-1-ylmethyl)stilbene 4,4'-dicarbonitrile, (Z)- $\alpha$ -(5-methylimidazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile, and (Z)-2-[2-(4-cyanophenyl)-4-(1,2,4-triazol-1-yl)-propenyl]pyridine-4-carbonitrile as disclosed in European Patent Application, Publication No. 299,683; (1R\*, 2R\*)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene, (1R\*, 2R\*)-6-fluoro-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)-naphthalene, (1R\*, 2R\*)-and (1R\*, 2S\*)-2-(4-fluorophenyl)1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene-6-carbonitrile, (1R\*, 2R\*)-and (1R\*, 2S\*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolylmethyl)naphthalene-6-carbonitrile, (1R\*, 2R\*)-and (1R\*, 2S\*)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-1-ylmethyl)naphthalene-2,6-

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dicarbonitrile, (1R\*,2R\*)-and (1R\*,2S\*)-1,2,3,4-tetrahydro-1-(1H-imidazol-1-ylmethyl)naphthalene-2,6-dicarbonitrile, and (1R\*,2S\*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-1-(4-methyl-1H-imidazolylmethyl)naphthalene-6-carbonitrile as disclosed in European Patent Application, Publication No. 281,283; 8-chloro-5-(4-chlorophenyl)-5H-indeno[1,2-d]pyridine as disclosed in U.S. Patent No. 4,769,378; 5-bis(4-chlorophenyl)methylpyrimidine as disclosed in U.S. Patent No. 4,762,836; 10-(2-propynyl)-estr-4-ene-3,17-dione as disclosed in U.S. Patent No. 4,322,416; 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole as described in European Patent Application, Publication No. 293,978; 1-methyl-androsta-1,4-dien-3,17-dione (Schering AG) as disclosed in U.S. Patent No. 4,591,585; 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione as disclosed in British Patent GB 2,151,266; 4-hydroxyandrostene-3,17-dione as disclosed in U.S. Patent No. 4,500,523; 4-(5,6,7,8-tetrahydroimidazo-[1,5- $\alpha$ ]pyridin-5-yl)benzonitrile (fadrazole) as disclosed in U.S. Patent No. 4,728,645, and 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]benzonitrile as disclosed in USP 4,978,672 both to Ciba-Geigy; 6-methyleneandrosta-1,4-diene-3,17-dione, 4-aminoandrostan-1,4,6-trien-3,17-dione and 4-aminoandrosta-4,6-diene-3,17-dione as disclosed in U.S. Patent No. 4,757,061; 3-(1H-imidazol-1-yl-methyl)-2-methyl-1H-indole-1-propanoic acid as disclosed in U.S. Patent No. 4,273,782; 5-[3-chlorophenyl)(1H-imidazol-1-yl)methyl]-1H-benzimidazole as disclosed in European Patent Application, Publication No. 260,744; 10 $\beta$ -thiiranylestr-4-ene-

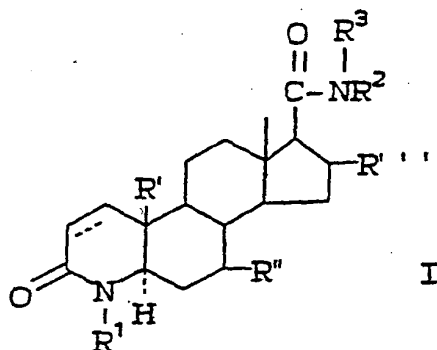


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- 3,17-dione and 10B-oxiranylestr-4-ene-3,17-dione as disclosed in J. Organ. Chem. 53: 5947-5951 (1988); 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione as described in U.S. Patent No. 4,668,689; 3-(4-aminophenyl)-3-ethylpyrrolidine-2,5-dione as disclosed in J. Med. Chem. 29: 520-523 (1986); 1-(7-carboxyheptyl)-imidazole as described in U.S. Patent No. 4,320,134; 1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]-furanone (1a) as disclosed in European Patent Application, Publication No. 316,097; 1,3,5-andros-tatriene-3,17-dione disclosed in Biochem. Pharmac. 31: 2017-2023 (1982) and other compounds well known in the art of aromatase inhibitor and cancer therapy such as bis-(p-cyanophenyl)-imidazo-1-yl-methane hemisuccinate and pharmaceutically acceptable derivatives, acid addition salts and possible stereochemically isomeric forms thereof, if and where appropriate.
- Preferred for use in the instant invention is fadrazole. The invention is also intended to include any biologically active equivalents of an aromatase inhibitor as described above.
- Preferred is where the 4-aza steroid has the formula:

30

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wherein the dotted line represents a double bond when present,  $R^1$  and  $R^3$  are independently hydrogen, methyl or ethyl,

$R^2$  is a hydrocarbon radical selected from straight or branched chain substituted or unsubstituted alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents,

$R'$  is hydrogen or methyl,

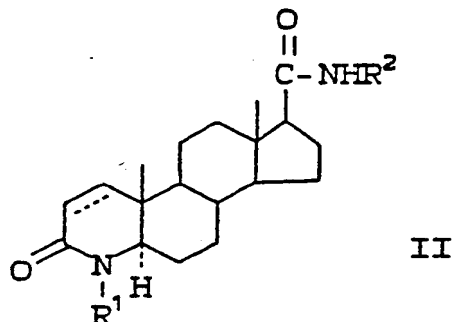
$R''$  is hydrogen or  $\beta$ -methyl,

$R'''$  is hydrogen,  $\alpha$ -methyl or  $\beta$ -methyl, and

pharmaceutically acceptable salts or esters thereof.

A preferred embodiment of the compound of formula I applicable in the process of our invention is represented by the formula:

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10

wherein

$R^1$  is hydrogen, methyl or ethyl, and

15  $R^2$  is branched chain alkyl cycloalkyl, aralkyl of from 4-12 carbons, phenyl, optionally substituted by methyl, chloro or fluoro, substituted or unsubstituted 1-, 2-adamantyl, 1-, 2-adamantylmethyl, 1-, 2- or 7-norbornanyl, 1-, 2- or 7-norbornanymethyl.

20

Representative compounds of the present invention include the following:

17B-(N-tert-amylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

17B-(N-tert-hexylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one.

25

17B-(N-tert-butylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

17B-(N-isobutylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

30

17B-(N-tert-octylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

17B-(N-octylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

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- 17B-(N-1,1-diethylbutylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-neopentylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
5 17B-(N-2-adamantylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-1-adamantylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
10 17B-(N-2-norbornylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-1-norbornylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-phenylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
15 17B-(N-benzylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-tert-amylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-tert-hexylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
20 17B-(N-tert-butylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-isobutylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
25 17B-(N-tert-octylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-1,1,3,3-tetramethylbutylcarbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,  
17B-(N-octylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,  
30 17B-(N-1,1-diethylbutylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one,

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- 17B-(N-neopentylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -androst-  
1-en-3-one,  
17B-(N-1-adamantylcarbamoyl)-4-aza-5 $\alpha$ -androstan-  
3-one;  
5 17B-(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 $\alpha$ -  
androst-1-en-3-one;  
17B-(N-1-adamantylcarbamoyl)-4-methyl-4-aza-  
5 $\alpha$ -androstan-3-one;  
17B-(N-1-adamantylmethylcarbamoyl)-4-aza-5 $\alpha$ -  
10 androst-1-en-3-one;  
17B-(N-2-adamantylcarbamoyl)-4-aza-5 $\alpha$ -androstan-  
3-one;  
17B-(N-methyl-N-2-adamantylcarbamoyl)-4-methyl-4-aza-  
androstan-3-one;  
15 17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-  
5 $\alpha$ -androstan-3-one;  
17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-  
5 $\alpha$ -androst-1-en-3-one;  
17B-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-  
20 androst-1-en-3-one;  
17B-(N-(3-methyl)-1-adamantyl-carbamoyl)-4-aza-4-  
methyl-5 $\alpha$ -androst-an-3-one;  
17B-(N-exo-2-norbornanylcarbamoyl)-4-aza-4-methyl-5 $\alpha$ -  
androst-1-en-3-one;  
25 17B-(N-exo-2-norbornanylcarbamoyl)-4-aza-5 $\alpha$ -androst-  
1-en-3-one; 17B-(N-2-adamantylcarbamoyl)-4-aza-5 $\alpha$ -  
androst-en-3-one;  
17B-(N-methyl-N-2-adamantylcarbamoyl)-4-aza-4-methyl-  
androstan-3-one;  
30 17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-  
5 $\alpha$ -androstan-3-one; and  
17B-(N-methyl-N-2-adamantyl)carbamoyl-4-methyl-4-aza-  
androst-1-en-3-one.

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The corresponding compounds of those above wherein the 4-aza substituent is substituted in each of the above named compounds with a hydrogen, methyl or an ethyl radical, to form a different N-substituent, and wherein a double bond can be optionally present as indicated by the dotted line in position 1.

The alkyl, cycloalkyl, aralkyl, monocyclic aryl, 1-, 2-adamantyl or 1-, 2-norbornanyl moieties can be substituted with one or more substituents of the following: C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl, including methyl, ethyl, isopropyl, n-butyl; nitro; oxo; C<sub>7</sub>-C<sub>9</sub> aralkyl, including benzyl; (CH<sub>2</sub>)<sub>n</sub> COOR where n is 0-2 and R is H or C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl including methyl, ethyl; CH<sub>2</sub>OH; OH; OR where R is C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl including methyl, ethyl; halo, including fluoro, bromo, iodo; COOH; COOR, where R is linear/branched C<sub>1</sub>-C<sub>4</sub> alkyl; -CONH<sub>2</sub>; CH<sub>2</sub>NH<sub>2</sub>; CH<sub>2</sub>NHCOR where R is C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl including methyl, ethyl; phenyl; o, m, p-substituted phenyl including p-nitro, p-amino and p-sulfo; or cyano. The amino group of the adamantyl or norbornanyl moiety can also be substituted as R<sup>1</sup> with methyl and ethyl, as well as hydrogen.

Also included within the scope of this invention are pharmaceutically acceptable salts or esters, where a basic or acidic group is present on the substituted alkyl, cycloalkyl, aralkyl, adamantyl or norbornanyl moiety. When an acidic substituent is

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present, i.e. -COOH, there can be formed the ammonium, sodium, potassium, calcium salt, and the like, for use as the dosage form.

5 Where a basic group is present, i.e. amino, acidic salts, i.e. hydrochloride, hydrobromide, acetate, pamoate, and the like, can be used as the dosage form.

10 Also, in the case of the -COOH group being present, pharmaceutically acceptable esters can be employed, e.g. acetate, maleate, pivaloyloxymethyl, and the like, and those esters known in the art for modifying solubility or hydrolysis characteristics for use as sustained release or prodrug formulations.

Representative examples include for R<sup>2</sup>  
15 (where AD is adamantyl):  
3, 5, 7-trinitro-1-AD; 4-oxo-1-AD; 1-benzyl-1-AD;  
4,4-dimethyl-1-AD; 3,7-dimethyl-5-carboxymethyl-1-AD;  
3-carboxymethyl-1-AD; 3-chloro-1-AD; 1,3-dihydroxy-  
6,6-dimethyl-2-AD; 3-chloro-1-AD; 4-carbethoxy-2-AD;  
20 4-carboxy-2-AD; 3-isopropyl-1-AD; 3-n-butyl-1-AD;  
3-propyl-1-AD; 3-,5-diethyl-1-AD; 3-hydroxymethyl-  
1-AD; 2-carboxy-1-AD; 3-methyl-1-AD; 5-hydroxy-2-AD;  
2-hydroxy-1-AD; 1-aminomethyl-1-hydroxy-2-AD;  
2-oxo-1-AD; 2-phenyl-2-AD; 1-amino-methyl-2-AD;  
25 1-carboxy-2-AD; 1-aminocarbonyl-2-AD; 3-hydroxy-  
5,7-dimethyl-1-AD; 4-fluoro-1-AD; 3-fluoro-1-AD;  
4-hydroxy-2-AD; 3-phenyl-1-AD; 3-(p-aminophenyl)-  
1-AD; 3-(p-nitrophenyl)-1-AD; 3-methyl-5-  
hydroxymethyl-1-AD; 3,5-dimethyl-4-hydroxy-1-AD;  
30 2-hydroxymethyl-2-AD; 3-(p-sulfophenyl)-1-AD; 3-  
methyl-5-ethyl-1-AD; 2-carboxy-2-AD; 3,5-7-trimethyl-  
1-AD; 4-iodo-2-AD; 4-bromo-2-AD; 4-chloro-2-AD;

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1-acetylaminoethyl-2-AD; 1-carboxymethyl-2-AD;  
1-methyl-2-AD; 1-aminocarboxymethyl-2-AD;  
1-aminocarboxyl-1-AD; 2-cyano-2-AD; 3,5-dimethyl-  
7-ethyl-1-AD; 4-hydroxy-1-AD; 1-hydroxy-2-AD;  
5 5-carboxy-3-methyl-1-AD; 3,5-dimethyl-7-carboxy-  
1-AD; 3-carboxy-1-AD; 3-hydroxy-1-AD; and the like.

Representative examples include for R<sup>2</sup> as  
substituted norbornanyl moieties are (where NB is  
norbornanyl):

10 2-NB; 1,7,7-trimethyl-4-phenyl-2-NB; 3-carboxy-2-  
NB; 3-phenyl-2-carboxy-2-NB; 2-cyano-3-phenyl-2-NB;  
3-hydroxy-4,7,7-trimethyl-2-NB; 6-hydroxymethyl-2-  
NB; 5-cyano-2-NB; 3-allyl-2-NB; 1-NB; 7,7-dimethyl-1-  
hydroxymethyl-2-NB; 3-methoxy-4,7,7-trimethyl-2-NB;  
15 3-aminocarbonyl-2-NB; 3-ethoxycarbonyl-2-NB; 3,3-  
dimethyl-2-NB; 7-oxo-1-NB; 3-phenyl-2-NB; 1-carboxy-  
methyl-7,7-dimethyl-2-NB; 1-ethyl-2-NB; 1-methyl-2-  
NB; 2,2,3,3,5,5,6,6,7,7-decafluoro-1-NB; 3-hydroxy-  
2-NB; 3-chloro-2-NB; 3-(p-methoxyphenyl)-2-NB; 2,2-  
20 dimethyl-3-methylene-7-NB; 3-oxo-2-NB; 1-methoxy-2-  
NB; 7-NB; 3-isopropyl-2-NB; 2-bromo-1-NB; 3-chloro-  
1-NB; and the like.

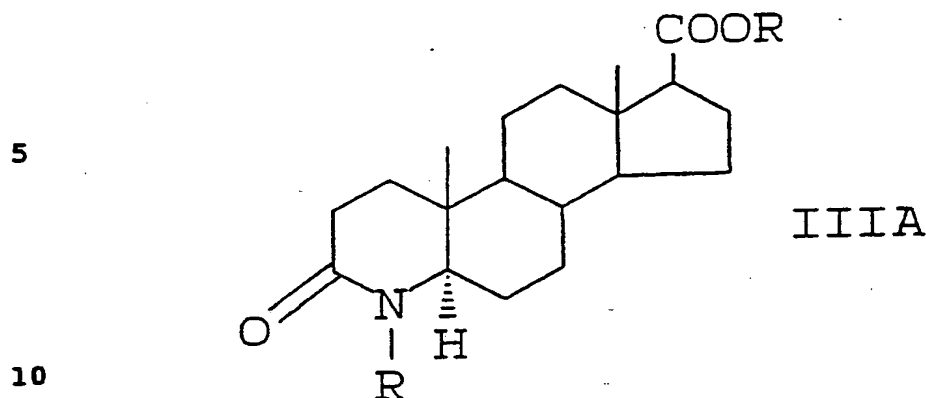
Procedures for preparing the compounds of  
Formula I useful in this invention, including the  
25 above, are well known in the art.

The novel compounds of formula I of the  
present invention can be prepared by a method  
starting with the known steroid ester (IIIA) of the  
formula:

30



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15 17 $\beta$ -(carbomethoxy)-4-aza-5- $\alpha$ -androstan-3-ones which includes the stages of optionally 1) dehydrogenating said starting material to produce the corresponding compound containing a double-bond in the 1,2-position of the A-ring, 2) converting the 17-carbomethoxy substituent into an N-substituted alkyl, cycloalkyl, aralkyl, monocyclic acyl, or adamantylcarbamoyl substituent and, if desired, 3) alkylating the A-ring

20 nitrogen to introduce a N-methyl or N-ethyl substituent into the A ring 4-position. For the dehydrogenatin step, it is preferable that the 4-aza nitrogen be unsubstituted. The alternate pathways can consist of one or more discrete chemical steps

25 and if desired can take place before step (1) or following step (1) or step (3).

In accordance with the process of the present invention (see flow sheet), the products of our invention are formed by optionally: (1) heating

30 a 17 $\beta$ -alkoxycarbonyl-4-aza-5 $\alpha$ -androstan-3-ones, com-

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pound III, (prepared in the literature as described in the reference US Patent 4,377,584) with a dehydrogenating agent such as benzeneseleninic anhydride in a refluxing inert solvent, e.g. chlorobenzene, to form a 17B-alkoxycarbonyl-4-aza-5 $\alpha$ -androst-1-ene-3-one IV (alternately, the dichlorodicyanobenzoquinone process of Dolling, et al., JACS 1988, Vol. 110, pp. 3318-3319, can be used); (2) the formed 5 $\alpha$ -androst-1-en-3-one compound from Step 1 can be reacted with, e.g. sodium hydride under anhydrous conditions in a neutral solvent such as dimethylformamide; (3) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17B-alkoxy-adamantyl-carbamoyl-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one V; (4) subsequently hydrolyzing said 17B-alkoxycarbonyl-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one with a strong base, such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid to yield 17B-carboxy 4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one VI; (5) said steroidal acid can be then converted to its corresponding 2-pyridylthio ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent such as toluene and the resulting product 17B-(2-pyridylthiocarbonyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one VII can be isolated by chromatography on e.g. silica gel; and (6) said pyridylthio ester can be then reacted with 1-adamantyl-, 2-adamantylamine or norbornanyllamine in an inert solvent e.g. tetrahydrofuran, to form the desired product 17B-N-adamantyl-

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carbamoyl-4-alkyl-4-aza-5 $\alpha$ -androsta-1-en-3-one VIII which can be isolated by chromatography e.g. on silica gel. When the previous reaction is carried out in the absence of first forming the double bond at position 1, the corresponding 17 $\beta$ -(N-adamantyl-carbamoyl)-4-alkyl-4-aza-5 $\alpha$ -androsta-3-one (or N-norbornanyl carbamoyl compound) is prepared.

In accordance with an alternate process of our invention the corresponding N-unsubstituted-17 $\beta$ -(N-adamantyl-carbamoyl)-4-aza-5 $\alpha$ -androsta-1-en-3-one XIV is readily prepared from the 17 $\beta$  (alkoxycarbonyl)-4-aza-5 $\alpha$ -androsta-3-one IV by repeating the above series of reaction steps but omitting the alkylation Step 2 herein above, i.e. treatment of the 4-aza-5 $\alpha$ -androsta-1-en-3-one with e.g. sodium amide followed by methyl or ethyl iodide via intermediates XII and XIII.

In accordance with a further alternate process of preparing the compounds of our invention having only hydrogen as the sole substituent on the ring A - nitrogen, the double bond in the A ring is introduced as the last step of the process. Thus, a 17 $\beta$ -alkoxycarbonyl 4-aza-5 $\alpha$ -androsta-3-one III is hydrolyzed to the corresponding steroidal acid IX 17 $\beta$ -carboxy-4-aza-5 $\alpha$ -androsta-3-one which in turn is converted to the corresponding pyridylthio ester, 17 $\beta$  (2-pyridylthiocarbonyl)-4-aza-5 $\alpha$ -androsta-3-one, X followed by treatment of the ester with an amine of formula R<sup>2</sup>-NH<sub>2</sub> wherein R<sup>2</sup> is as defined hereinabove as 1- or 2-adamantyl or 1-, 2-, or 7-norbornanyl

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to form a 17B (N-adamantyl-carbamoyl)-4-aza-5 $\alpha$ -androstone-3-one XI which is dehydrogenated as previously described to produce compound XIV, 17B-(N-adamantyl-carbamoyl)-4-aza-androst-1-en-3-one or corresponding norbornanyl derivative.

In another alternate method of introducing the 17B-(N-adamantyl-carbamoyl)substituent into a 17B-carboxy androstane compound of formula VI, XII or IX, each is treated in a manner similar to the procedure described in Steroids, Vol. 35 #3, March 1980, p. 1-7 with dicyclohexylcarbodiimide and 1-hydroxybenzo-triazole to form the 17B-(1-benzotriazoloxycarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one, VII, XIII or compound X, wherein the substituent X is benzotriazoloxo group.

The 16-methyl derivative wherein R''' is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5 $\alpha$ -androstan-3-ones, e.g. 4,16 $\beta$ -dimethyl-17 $\beta$ -acetyl-4-aza-5 $\alpha$ -androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16 $\beta$ -dimethyl-17 $\beta$ -acetyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

The above reactions are schematically represented in the following flowsheet.

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Flowsheet

5

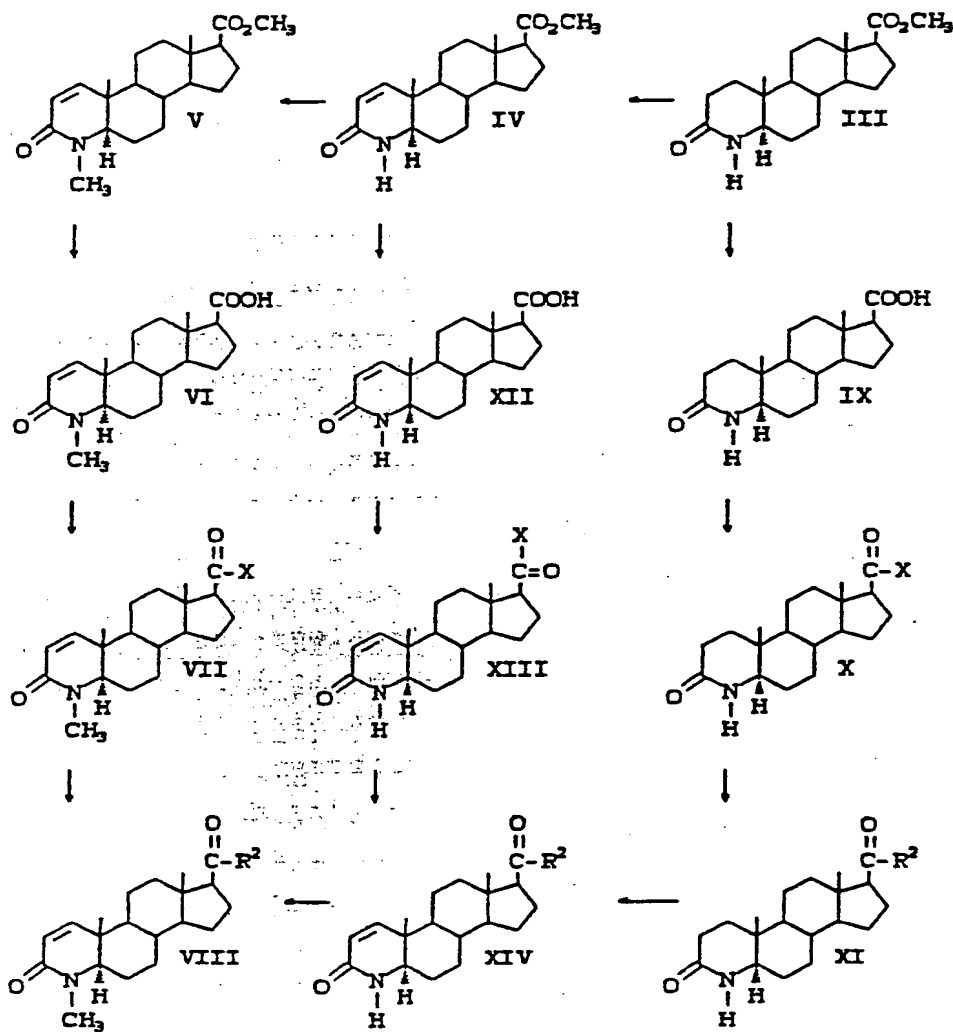
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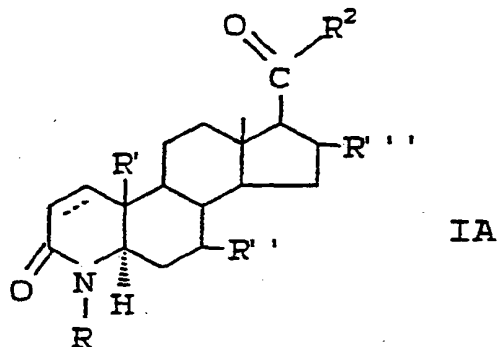


X is 2-pyridylthio or 1-benzotriazoloxy.

R<sup>2</sup> is 1- or 2-adamantyl or norbornanyl.

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Also a preferred 4-azasteroid is a 17 $\beta$ -acyl-4-aza-5 $\alpha$ -androst-1-ene-3-one compound of the formula:



15 wherein the dotted line represents a double bond when present;

R is selected from hydrogen, methyl and ethyl;

R<sup>2</sup> is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C<sub>1</sub>-C<sub>2</sub> alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

(c) a polycyclic aromatic radical which can be substituted with one or more of: -OH, protected -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>, COOH, including protected hydroxy, where m is 1-4, n is

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1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present when one of the above oxygen-containing radicals is present;

5 (2) -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -SOC<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl -(CH<sub>2</sub>)<sub>m</sub>SH, -S-(CH<sub>2</sub>)<sub>n</sub>-O-COCH<sub>3</sub>, where m is 1-4 n is 1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present  
10 when one of the above sulfur containing radicals is present;

(3) N(R<sup>3</sup>)<sub>2</sub>, which can be protected, where R<sup>3</sup> is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl, where the monoaryl ring can also be further substituted with C<sub>1</sub>-C<sub>4</sub> alkyl; and  
15

(4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;  
20

and R', R'' and R''' are each selected from hydrogen and methyl, and pharmaceutically acceptable salts thereof.

25

A preferred embodiment of the compounds of our invention process is:

the compound of above Structure IA,  
30 wherein the dotted line is a double bond,  
R is hydrogen or methyl, and

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R<sup>2</sup> is branched chain alkyl, or cycloalkyl of from 4-10 carbons, and R' and R''' are hydrogen.

Another embodiment of the invention is the compounds of above Structure I where R<sup>2</sup> is phenyl, or phenyl substituted by substituents described above, including where

R<sup>2</sup> is phenyl, 2-, 3-, or 4-tolyl, xylyl, 2-bromophenyl, 2-chlorophenyl, 2,6-dichlorophenyl, 2,6-dibromophenyl, aminophenyl, N-alkylaminophenyl, N-N-dialkylaminophenyl, 4-biphenyl, 3-biphenyl, naphthyl, anthracyl, phenanthryl, thiophenyl, methylthiophenyl, methylsulfinyl, phenyl, methylsulfofenyl, aminosulfofenyl, thioethylphenyl, acetoxymethylthiophenyl, 17B-(4-hydroxyphenyl), 17B-(3-hydroxyphenyl), 17B-(3,4-dihydroxyphenyl), or 17B-(3,5-dimethyl-4-hydroxyphenyl).

Representative compounds of the invention are:

17B-(phenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;

17B-(2-tolylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;

17B-(3-tolylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;

17B-(4-tolylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;

17B-(2-bromophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;

17B-(2-chlorophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;



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- 17B-(2,6-dichlorophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2,6-dibromophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;  
5 17B-(xylylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-ene-3-one;  
17B-(t-butylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(isobutylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(isooctylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
10 17B-(n-octylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(1,1-diethylbutylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(neopentylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(tert-amylcarbonyl)-4-aza-4-5 $\alpha$ -androst-1-ene-3-one;  
15 one;  
17B-(tert-hexylcarbonyl)-4-aza-4-5 $\alpha$ -androst-1-ene-3-one;  
one;  
17B-(cyclohexylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
one;  
20 17B-(cyclopentylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
one;  
17B-(benzylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2-pyridylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(4-pyridylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
25 17B-(2-pyrrolylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
one;  
17B-(2-furylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2-thiophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
one;  
30 17B-(2-adamantylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
one;

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- 17B-(phenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2-tolylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(3-tolylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(4-tolylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
5 17B-(2-bromophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2-chlorophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
10 17B-(2,6-dichlorophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(2,6-dibromophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(xylylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
17B-(phenylethyl)carbonyl-4-aza-5 $\alpha$ -androst-1-ene-3-one;  
15 one;  
17B-(4-dimethylaminophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(3-dimethylaminophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one.  
20 17B-(3,4-diethylaminophenylcarbonyl)-4-aza-androst-1-en-3-one.  
17B-(3,5-dimethyl-4-diethylaminophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-N-methylaminomethylphenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one; or  
25 17B-(2-N-ethylamino-4-ethylphenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one.  
17B-(4-phenylbenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(3-phenylbenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
30 17B-(4-biphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;

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- 17B-(3-biphenyl)-4-aza-5a-androst-1-en-3-one;  
17B-(1-naphthyl)-4-aza-5a-androst-1-en-3-one;  
17B-(2-naphthyl)-4-aza-5a-androst-1-en-3-one;  
17B-(1-phenanthryl)-4-aza-5a-androst-1-en-3-one;  
5 17B-(2-phenanthryl)-4-aza-5a-androst-1-en-3-one;  
17B-(1-biphenyl)-4-aza-5a-androst-1-en-3-one;  
17B-(9-anthracyl)-4-aza-5a-androst-1-en-3-one;  
17B-(4-thiophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
10 17B-(3-thiophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-methylthiophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-methylsulfinylphenylcarbonyl)-4-aza-5 $\alpha$ -  
15 androst-1-en-3-one;  
17B-(4-methylsulfophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(3-methylsulfinylphenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
20 17B-(4-N,N-dimethylaminosulfophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(2-ethyl-4-methylthiophenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-thioethylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -  
25 androst-1-en-3-one;  
17B-(4-acetoxymethylthiophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
17B-(2-methyl-4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
30 17B-(2-methyl-4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;

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- 17B-(2-isopropyl-4-methylsulfonylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-methylthiophenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-3-one;  
5 17B-(4-methylsulfinylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-3-one;  
17B-(4-methylsulfonylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -androst-3-one;  
17B-(4-hydroxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
10 17B-(3-hydroxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(3,4-dihydroxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
15 17B-(4-hydroxymethylphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(2-hydroxyethylphenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-methoxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
20 17B-(4-carboxymethylphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one;  
17B-(4-hydroxyphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
17B-(3-hydroxyphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
25 17B-(3,4-dihydroxyphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
17B-(3,5-dimethyl-4-hydroxyphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;  
30 17B-(4-hydroxymethylphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one;

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17B-(2-hydroxyethylphenylcarbonyl)-4-aza-4-methyl-5 $\alpha$ -  
androst-1-en-3-one;

17B-(4-methoxyphenyl)-4-aza-4-methyl-5 $\alpha$ -androst-1-en-  
3-one;

5 17B-(4-carboxymethylphenyl)-4-aza-4-methyl-5 $\alpha$ -  
androst-1-en-3-one; and

17B-(4-carboxyphenyl)-4-aza-5 $\alpha$ -androst-1-en-3-one,

and the corresponding compounds wherein the

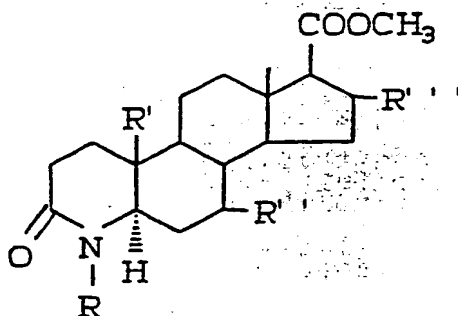
4-hydrogen substituent is replaced in each of the

10 above named compounds by a methyl or an ethyl radical.

The compounds of formula IA of the present  
invention are prepared by a method starting with the  
known steroid ester of the formula:

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named 17B-(carbomethoxy)-4-aza-5 $\alpha$ -androstan-3-one,

which includes the stages of (1) dehydrogenating said

starting material to produce the corresponding com-

ound containing a double bond in the 1,2-position of

the A-ring, (2) converting the 17-carbomethoxy substi-

30 tuent into a 17B-acyl substituent and, if desired (3)

alkylating the A-ring nitrogen to introduce 4-methyl

- 32 -

or 4-ethyl substituents into the A-ring. For the dehydeogenation step, it is preferable that the 4-aza nitrogen be unsubstituted. The dehydrogenation step can be carried out, e.g. according to the procedure of Dolling, et al. involving dichlorodicyanobenzoquinone, JACS (1988) Vol. 110, pp. 3318-3319. Stage (2) may consist of one or more chemical steps and if desired may take place before stage (1) or following stage (1) or stage (3).

In accordance with the process of the present invention, the products of our invention are formed by (1) heating a 17B-alkoxycarbonyl-4-aza-5 $\alpha$ -androst-3-one compound III with a dehydrogenating agent such as benzeneseleninic anhydride in refluxing chlorobenzene to form a 17B-alkoxycarbonyl-4-aza-5 $\alpha$ -androst-1-en-3-one (IV), (2) the formed 5 $\alpha$ -androst-1-en-3-one compound from step (1) is reacted with sodium hydride and under anhydrous conditions in a neutral solvent such as dimethylformamide, (2) contacting the resulting reaction mixture with an alkyl (methyl or ethyl) iodide to form the corresponding 17B-alkoxycarbonyl-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (V), (3) subsequently hydrolyzing said 17B-alkoxycarbonyl-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one with a strong base such as aqueous methanolic potassium hydroxide at the reflux temperature, followed by acidification and isolation of the resulting steroidal acid, 17B-carboxy-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (VI), (4) said steroidal acid is then converted to its corresponding 2-thiopyridyl ester by refluxing with triphenyl phosphine and 2,2'-dipyridyl disulfide in an inert solvent and the product 17B-(2-

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pyridylthiocarbonyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (VII) is isolated by chromatography on silica, (5) said pyridylthio ester is then reacted with an R<sup>2</sup>-Li or an R<sup>2</sup>MgX (X=Cl, Br) compound, such as sec-butylmagnesium chloride in tetrahydrofuran, to form the desired product, e.g., 17B-(sec-butylcarbonyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When the previous reaction is carried out using an R<sup>2</sup>MgX or, an R<sup>2</sup>-Li compound in place of sec-butylmagnesium chloride, the corresponding 17B-(acyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one is prepared wherein acyl is R<sup>2</sup> carbonyl.

In accordance with the process of our invention, the corresponding 17B-acyl-4-aza-5 $\alpha$ -androst-1-en-3-one XV is readily prepared from the 17B(alkoxycarbonyl)-4-aza-5 $\alpha$ -androsten-3-one (IV) by repeating the above series of reaction steps but omitting step 2 hereinabove, i.e., treatment of the 4-aza-5 $\alpha$ -androst-1-en-3-one with sodium amide followed by methyl or ethyl iodide.

In accordance with a further alternate process of preparing the compounds of our invention, having only hydrogen as the sole substituent on the ring A-nitrogen, the 1,2-double bond in the A-ring is introduced as the last step of the process. Thus, a 17B-alkoxycarbonyl-4-aza-5 $\alpha$ -androstan-3-one (III) is hydrolyzed to the corresponding steroidal acid, 17B-carboxy-4-aza-5 $\alpha$ -androstan-3-one, (IX) which, in turn, is converted to the corresponding thiopyridyl ester, 17B-(2-pyridylthiocarbonyl)-4-aza-5 $\alpha$ -

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androstan-1-one (X) followed by treatment of the ester with an  $R^2MgX$  or  $R^2Li$  compound wherein  $R^2$  is as defined hereinabove to form a 17 $\beta$ -(acyl)-4-aza-5 $\alpha$ -androstan-3-one (XI) which is dehydrogenated as previously described to produce compound XIV, 17 $\beta$ -(acyl)-4-aza-5 $\alpha$ -androst-1-en-3-one.

In an additional alternative process for making the compounds of formula I when the starting material is an ester, particularly methyl ester as shown in formula III-V in the schematic, reaction with a Grignard reagent  $R^2MgX$ , gives the ketone, 17 $\beta$ - $R^2CO$ -, corresponding to the  $R^2$  moiety associated with the Grignard reagent.

The 16-methyl derivative wherein  $R'''$  is methyl are prepared from known 16-methyl-17-acyl-4-methyl-4-aza-5 $\alpha$ -androstan-3-ones, e.g. 4,16 $\beta$ -dimethyl-17 $\beta$ -acetyl-4-aza-5 $\alpha$ -androstan-3-one by known dehydrogenation procedures for 4-methyl-4-aza compounds to produce the corresponding 4,16 $\beta$ -dimethyl-17 $\beta$ -acetyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

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The above reactions are schematically represented in the following structural outline:

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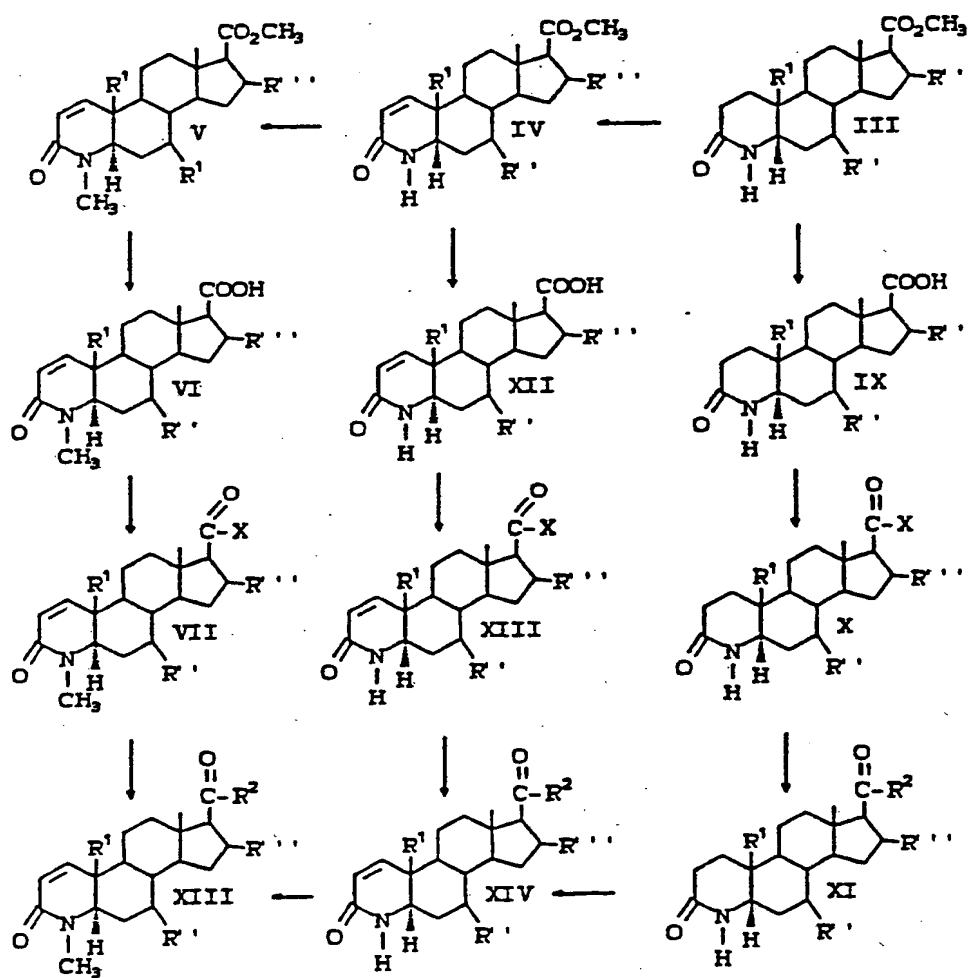
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X is 2-pyridylthio

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wherein X is a 2-pyridylthio substituent and  $R^2$  is defined as hereinabove.

In the above described reaction Scheme, where  $R^2$  is p-hydroxybiphenyl, this can be derived by starting with an appropriate bromobiphenylphenol, e.g. p-bromobiphenylphenol, protecting the phenolic -OH with a conventional blocking group, e.g. triorganosilyl, i.e. t-butyldimethylsilyl, carrying out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Preferred are the triorganosilyl groups, e.g. t-butyl-dimethylsilyl, phenyldimethylsilyl, diphenylmethyl-silyl, and the like.

By the term " $C_1$ - $C_4$  alkyl" is used herein, is meant linear or branched alkyl, including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, sec-butyl and t-butyl.

When this reaction scheme is carried out using an  $R^2MgX$  or  $R^2-Li$  compound containing an thiophenyl substituted  $R^2$ , e.g. p-methylthiophenyl

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magnesium chloride, the corresponding 17 $\beta$ -(substituted thio-benzoyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one is prepared wherein phenyl is R<sup>2</sup>.

5 The Grignard reagent, R<sup>2</sup>MgX, for all the species included within the scope of this invention, are available or can readily be made by one skilled in the art. For example, where R<sup>2</sup> is C<sub>1</sub>-C<sub>4</sub> alkyl thiophenyl, can be formed from the appropriate C<sub>1</sub>-C<sub>4</sub> alkyl thiobromobenzene, e.g. p-methylthiobromobenzene.

10 The formed C<sub>1</sub>-C<sub>4</sub> alkyl thiobenzene can be used to further prepare C<sub>1</sub>-C<sub>4</sub> alkyl sulfoxides by oxidation with e.g. m-chloroperbenzoic acid. The resulting sulfoxide can be further oxidized by the use of the m-chloroperbenzoic acid reaction to  
15 proceed for a longer period of time to form the C<sub>1</sub>-C<sub>4</sub> alkyl sulfone.

Further, the sulfoxide can be used in the Pummerer rearrangement to form the corresponding thiol.

20 The -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub> alkyl)<sub>2</sub> substituted phenyl (R<sup>2</sup>) is formed from the appropriate bromobenzene, e.g. p-N,N-dimethylaminosulfobromobenzene which is used directly in the Grignard reaction to form the final product.

25 The thioalkyl groups on the phenyl ring, i.e. -(CH<sub>2</sub>)<sub>m</sub>SH, where m is 1-4, are readily formed via a four step procedure from an alkoxy alkyl phenyl bromide, Br-C<sub>6</sub>H<sub>4</sub>-(CH<sub>2</sub>)<sub>m</sub>OCH<sub>3</sub>. Direct addition of the Grignard reagent prepared from above-bromoalkyl  
30 phenyl derivative to the thiopyridyl ester results in

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the keto derivative, i.e. 17B(4-methoxyalkyl-benzoyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one. This can be readily converted into thio analogue via BBr<sub>3</sub> at -70°C to form the hydroxyalkyl derivative, followed by displacement by halogen, e.g. bromo and then converting the halogenated compound through NaSH displacement to give the final mercapto compound. Where in the Reaction Scheme said pyridylthio ester is reacted with an aminophenyl containing R<sup>2</sup>-Li or an R<sup>2</sup>MgX (X=Cl, Br) compound, such as p-dimethylaminophenyl magnesium chloride, this is carried out in tetrahydrofuran to form the desired product 17B-(p-dimethylaminophenyl-carbonyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel.

The Grignard reagent, R<sup>2</sup>MgX, for all of the aminophenyl species included within the scope of this invention, are available and can be made readily by one skilled in the art.

Where in the process said Grignard reagent contains a phenolic type R<sup>2</sup> moiety, then said pyridylthio ester is then reacted with an R<sup>2</sup>-Li or an R<sup>2</sup>MgX (X=Cl, Br) Grignard reagent, such as p-methoxyphenyl-magnesium chloride in tetrahydrofuran to form the desired product, e.g. 17B-(p-methoxyphenylcarbonyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one (VIII) which is isolated by chromatography on silica gel. When this reaction is carried out using another R<sup>2</sup>MgX or, an R<sup>2</sup>-Li compound in place of p-methoxyphenylmagnesium chloride, the corresponding 17B-(substituted benzoyl)-4-alkyl-4-aza-5 $\alpha$ -androst-1-en-3-one is prepared wherein phenyl is R<sup>2</sup>.

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The Grignard reagent,  $R^2MgX$ , for all of the species included within the scope of this invention, are available and can be made readily by one skilled in the art.

5           For example, where  $R^2$  is hydroxyphenyl, this can be derived by starting with an appropriate bromophenol, e.g. p-bromophenol, protecting the phenolic -OH with a conventional blocking group, e.g. triorganosilyl, i.e. t-butyldimethylsilyl, carrying  
10           out the Grignard reaction and then deblocking the silyl group by the use of, e.g. refluxing aqueous tetrabutylammonium fluoride.

          For  $R^2$  being hydroxyethylphenyl, the same blocking procedure can be analogously conducted  
15           starting with the appropriate hydroxyalkyl bromophenol, e.g. p-hydroxymethylbromobenzene, or p-hydroxyethylbromobenzene.

          Where  $R^2$  is carboxyphenyl, this can be obtained by the chromic acid oxidation of the  
20           appropriate hydroxymethylbenzene, e.g. p-bromo-hydroxymethylbenzene, formed as described above.

          Where  $R^2$  is  $-O-C_1-C_4$  alkyl, the appropriate bromo- $O-C_1-C_4$  alkyl benzene, e.g. p-methoxybromo-  
25           benzene, is utilized for the Grignard reaction.

          Other halo substituted benzenes to form the appropriate Grignard reagent useful in the instant invention will be obvious to one skilled in the art from this disclosure.

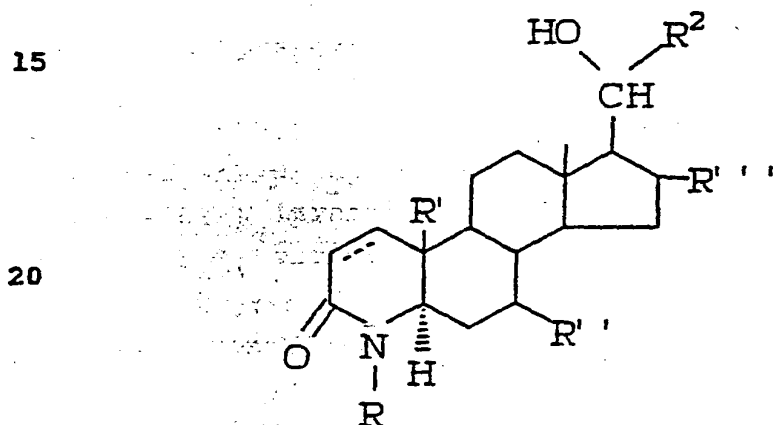
30           By the term "protected hydroxy" as used herein, is meant the alcoholic or carboxylic -OH

- 40 -

groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York.

5 Preferred are the triorganosilyl groups, e.g. t-butyl-dimethylsilyl, phenyldimethylsilyl, diphenylmethylsilyl, and the like.

Also within the scope of the present invention is the use of ketone reduction products of  
10 IA, in combination with an aromatase inhibitor for treatment of BPH being secondary alcohols of the formula:



wherein R is selected from hydrogen, methyl and ethyl;

R<sup>2</sup> is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which  
30 can be substituted by one or more of C<sub>1</sub>-C<sub>2</sub> alkyl or halo;

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- (b) an aralkyl radical selected from benzyl or phenethyl;
- (c) a polycyclic aromatic radical which can be substituted with one or more of:
- 5 -OH, protected -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, halo or nitro;
- (d) a monocyclic aromatic radical which can be substituted with one or more of:
- 10 (1) -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>COOH, including protecting hydroxy, where m is 1-4, n is 1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present when one of the above
- 15 oxygen-containing radicals is present;
- (2) -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -SOC<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl -(CH<sub>2</sub>)<sub>m</sub>SH, -S-(CH<sub>2</sub>)<sub>n</sub>-O-
- 20 COCH<sub>3</sub>, where m is 1-4 n is 1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present when one of the above sulfur containing radicals is present;
- 25 (3) N(R<sup>3</sup>)<sub>2</sub>, which can be protected, where R<sup>3</sup> is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl, where the monoaryl ring can also be further substituted with C<sub>1</sub>-C<sub>4</sub> alkyl;
- 30 and

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- (4) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

5           R', R'' and R''' are hydrogen or methyl, wherein the dotted line represents a double bond which can be present, and pharmaceutically acceptable salts and esters thereof.

10

          These compounds can be made by conventional sodium borohydride reduction of the carbonyl attached to R<sup>2</sup> without reducing the amide carbonyl in Ring A or the 1,2-double bond, if present. If the R<sup>2</sup> phenyl  
15       contains a carbonyl function, it can be selectively blocked and then regenerated after the borohydride reduction by conventional methods.

          The borohydride reduction can be carried out in, e.g. water or aqueous methanol, at a temperature  
20       of room temperature to 50°C and the product then isolated and purified by conventional means. The compounds are also active as 5-alpha reductase inhibitors in the treatment of patterned alopecia.

          The compounds of the present invention,  
25       prepared in accordance with the method described above, are, as already described, potent agents in combination with an aromatase inhibitor for the treatment of BPH.

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In this invention, the aromatase inhibitor, and the 5 $\alpha$ -reductase inhibitor are administered in combination separately or as one single combined pharmaceutical composition via parenteral or oral means. Preferably the aromatase inhibitor and the 5 $\alpha$ -reductase inhibitor are administered orally as separate compositions.

The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors.

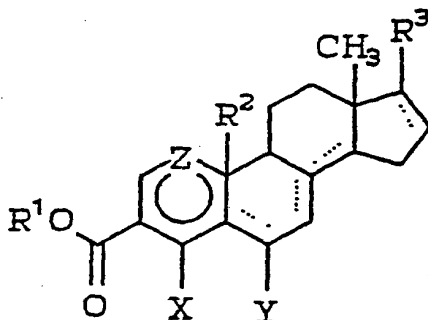
The aromatase inhibitor compositions are generally administered in a dosage range of about 10 to 400 mg/kg (body weight) per day with 50 to 250 mg per day in a single dose being preferred.

17 $\beta$ -substituted steroidal 5 $\alpha$ -reductase inhibitors which are non-4-aza steroids are known in the art and include those developed by SmithKline Beckmann as disclosed in U.S. Pat. 4,882,319 to Holt, et al.; U.S. Pat. 4,910,226 to Holt, et al; EPO Publn. 0 289 327 now USP 4,910,226; EPO Publn. 0 277 002 now USP 4,888,336; EPO Publn. 0 343 954; EPO Publn. 0 375 344 now USP 4,937,237; EPO Publn. 0 375 347; now USP 4,970,205; EPO Publn. 0 375 349; now USP 5,026,882.

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In the method the 17 $\beta$ -substituted non-aza steroids are of the formula:



in which:

the A ring has up to 2 double bonds;

the B, C, and D rings have optimal double bonds where indicated by the broken lines, provided that the A, B, and C rings do not have adjacent double bonds and the D ring does not have a C<sub>16</sub>-C<sub>17</sub> double bond when R<sub>3</sub> represents two substituents or a divalent substituent;

Z is (CH<sub>2</sub>)<sub>n</sub> and n is 0 or 2, provided that Z is (CH)<sub>n</sub> when adjacent to a double bond;

X is H, Cl, F, Br, I, CF<sub>3</sub>, or C<sub>1-6</sub>alkyl;

Y is H, CF<sub>3</sub>, F, Cl, or CH<sub>3</sub>, provided that Y is H when there is no C<sub>5</sub>-C<sub>6</sub> double bond;

R<sup>1</sup> is H or C<sub>1-8</sub>alkyl;

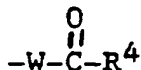
R<sup>2</sup> is absent or present as H or CH<sub>3</sub>, provided R<sup>2</sup> is absent when the carbon to which it is attached is unsaturated; and

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R<sup>3</sup> is(1)  $\alpha$ -hydrogen, or  $\alpha$ -hydroxyl, or  $\alpha$ -acetoxy  
and/or

(a)

5

where W is a bond or C<sub>1-12</sub> alkylidene, andR<sup>4</sup> is

10

(i) hydrogen,

(ii) hydroxyl,

(iii) C<sub>1-8</sub>alkyl,(iv) hydroxylic C<sub>1-8</sub>alkyl,(v) C<sub>1-8</sub>alkoxy,

15

(vi) NR<sup>5</sup>R<sup>6</sup>, where R<sup>5</sup> and R<sup>6</sup> are each  
independently selected from  
hydrogen, C<sub>1-8</sub>alkyl,C<sub>3-6</sub>cycloalkyl, phenyl; or R<sup>5</sup> and  
R<sup>6</sup> taken together with the

20

nitrogen to which they are  
attached represent a 5-6 membered  
saturated ring,(vii) OR<sup>7</sup>, where R<sup>7</sup> is hydrogen, alkali  
metal, C<sub>1-8</sub>alkyl, benzyl, or

25

(b) -Alk-OR<sup>8</sup>, where Alk is C<sub>1-12</sub>  
alkylidene, and R<sup>8</sup> is(i) phenyl C<sub>1-6</sub>alkylcarbonyl,(ii) C<sub>5-10</sub> cycloalkylcarbonyl,

(iii) benzoyl,

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(iv) C<sub>1-8</sub> alkoxy carbonyl,(v) aminocarbonyl, or C<sub>1-8</sub>alkyl  
substituted aminocarbonyl,

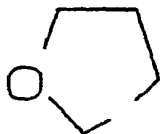
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(vi) hydrogen, or

(vii) C<sub>1-8</sub> alkyl,

(2) =CH-W-CO-R<sup>4</sup> or =CH-W-OR<sup>8</sup>, where W is a bond of C<sub>1-12</sub> alkylidene and R<sup>4</sup> and R<sup>8</sup> have the same meaning as above and R<sup>8</sup> also is hydrogen or C<sub>1-20</sub> alkylcarbonyl,

(3)



where the dashed bond replaces the 17- $\alpha$ -hydrogen,

(4)  $\alpha$ -hydrogen and NHCOR<sup>9</sup> where R<sup>9</sup> is C<sub>1-12</sub>alkyl or NR<sup>5</sup>R<sup>6</sup> where R<sup>5</sup> and R<sup>6</sup> have the same meaning as above,

(5)  $\alpha$ -hydrogen and cyano,(6)  $\alpha$ -hydrogen and tetrazolyl, or

(7) keto;

or a pharmaceutically acceptable salt thereof; except compounds in which:

(i) the B ring has a C<sub>5</sub>-C<sub>6</sub> double bond, R<sup>1</sup> is CH<sub>3</sub>, and R<sup>3</sup> is keto, methoxycarbonyl, or acetyl; or

(ii) the A-nor ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>3</sup> is acetoxy or acetyl;

(iii) R<sup>1</sup> is CH<sub>3</sub> and R<sup>3</sup> is acetoxy or acetyl; or

(iv) the A-nor ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>1</sup> is methyl; or

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(v) the B ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>3</sup> is B-hydroxy.

5 Representative compounds whose synthesis and properties are disclosed in the above issued US patents include the following and pharmaceutically acceptable salts thereof:

- 10 4-methyl-4-aza-5a-8(14)-pregnen-3-one-(20R)-20-carboxylic acid;  
(20R)-hydroxymethyl-4-methyl-4-aza-5a-8(14)-pregnen-3-one;  
4-methyl-4-aza-5a-8(14)-androsten-3-one-17B-N,N-diisopropylcarboxamide;
- 15 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-triene-3-phosphonic acid;  
17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-phosphonic acid;  
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-
- 20 tetraene-3-phosphonic acid;  
17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-tetraene-3-phosphonic acid;  
17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-
- 25 pentaene-3-phosphonic acid;  
17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5(10)triene-3-phosphonic acid;  
17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5(10)-triene-3-phosphonic acid;
- 30 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-tetraene-3-phosphonic acid;  
17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5(10)-triene-3-phosphonic acid;

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- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5  
(10)-triene-3-phosphonic acid;
- 17B-(N-butylcarboxamide)-estr-1,3,5(10)-triene-3  
carboxylic acid;
- 5 17B-(N-butylcarboxamide)-estr-1,3,5(10)16-tetraene-  
3-carboxylic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-  
triene-3-phosphinic acid;
- 10 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-  
3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5  
(10)-triene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5  
(10)-triene-3-phosphinic acid;
- 15 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5  
(10)-triene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5  
(10)-triene-3-phosphinic acid;
- 20 17B-(N,N-diisopropylcarboxamide)-1,3,5(10),16-  
tetraene-3-phosphinic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-  
tetraene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-  
pentaene-3-phosphinic acid;
- 25 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-  
tetraene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-  
triene-3-phosphonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-  
phosphonic acid;
- 30 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-  
tetraene-3-phosphonic acid;

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- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-tetraene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-pentaene-3-phosphonic acid;
- 5 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5(10)-triene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5(10)-triene-3-phosphonic acid;
- 10 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6-tetraene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5(10)-triene-3-phosphonic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5(10)-triene-3-phosphonic acid;
- 15 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10)-triene-3-sulfonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10)-triene-3-sulfonic acid;
- 20 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),16-tetraene-3-sulfonic acid;
- 17B-(N-tert-butylcarboxamide)-estr-1,3,5(10),16-tetraene-3-sulfonic acid;
- 25 17B-(N,N-diisopropylcarboxamide)-estr-1,3,5(10),6,8-pentaene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-2-methyl-estr-1,3,5(10)-triene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-methyl-estr-1,3,5(10)-triene-3-sulfonic acid;
- 30 17B-(N,N-diisopropylcarboxamide)-2-chloro-estr-1,3,5(10)-triene-3-sulfonic acid;
- 17B-(N,N-diisopropylcarboxamide)-4-chloro-estr-1,3,5(10)-triene-3-sulfonic acid;

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- 17B-(N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphinic acid;
- 17B-(N-t-butylcarboxamide)-androst-3,5-diene-3-phosphinic acid;
- 5 17B-(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-3-ene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-2-ene-3-phosphinic acid;
- 10 17B-(N,N-diisopropylcarboxamide)-androst-2,4-diene-3-phosphinic acid;
- methyl(17B-N,N-diisopropylcarboxamide)-androst-3,5-diene-3-phosphinic acid;
- 20 $\alpha$ -(hydroxymethyl)-5 $\alpha$ -pregn-3-ene-3-phosphinic acid;
- 15 17B-(N,N-diisopropylcarboxamide)-4-fluoro-5 $\alpha$ -androst-3-ene-3-phosphinic acid;
- 20 $\alpha$ -(hydroxymethyl)-4-fluoro-5 $\alpha$ -pregn-3-ene-3-phosphinic acid;
- 20 $\alpha$ -(hydroxymethyl)-A-nor-5 $\alpha$ -pregn-1-ene-2-phosphinic acid;
- 20 17B-(N,N-diisopropylcarboxamide)-5 $\alpha$ -androst-1,3-diene-3-phosphinic acid;
- 17B-(N,N-diisopropylcarboxamide)-5 $\alpha$ -androstane-3 $\beta$ -phosphinic acid;
- 25 17B-(N,N-diisopropylcarboxamide)-estr-3,5(10)-diene-3-phosphinic acid;
- 17B-(N,N-Diisopropylcarboxamide)-estr-3,5-diene-3-phosphinic acid;
- 17B-(N,N-Diisopropylcarboxamide)-androst-3,5-11-triene-3-phosphinic acid.
- 30 20 $\alpha$ -(hydroxymethyl)-5 $\alpha$ -pregn-3-ene-3-carboxylic acid;



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- N,N-diisopropyl-5 $\alpha$ -androst-3-ene-17 $\beta$ -carboxamide-3 carboxylic acid;  
N,N-diisopropyl-androst-3,5-diene 17 $\beta$ -carboxamide-3-carboxylic acid;  
5 17 $\beta$ -(N,N-diisopropylcarboxamide)-4-fluoro-5 $\alpha$ -androst-3-ene-3-carboxylic acid;  
20 $\alpha$ -(hydroxymethyl)-4-fluoro-5 $\alpha$ -pregn-3-ene-3-carboxylic acid;  
20 $\alpha$ -(hydroxymethyl)-A-nor-5 $\alpha$ -pregn-1-ene-2-carboxylic acid;  
10 17 $\beta$ -N,N-diisopropylcarboxamide-5 $\alpha$ -androst-1,3-diene-3-carboxylic acid;  
N-t-Butyl Androst-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid;  
15 N,N-Diisopropyl-5 $\alpha$ -Androst-2-ene-17-B-carboxamide-3-carboxylic acid;  
N,N-Diisopropyl Androst-2,4,-diene-17 $\beta$ -carboxamide-3-carboxylic acid;  
N,N-Diisopropyl 5 $\alpha$ -Androstane-17 $\beta$ -carboxamide  
20 carboxylic acid;  
N,N-Diisopropyl Estr-3,5(10)-diene-17 $\beta$ -carboxamide-3-carboxylic acid;  
N,N,-Diisopropyl Estr-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid;  
25 20 $\alpha$ (hydroxymethyl)-5 $\alpha$ -pregn-3-ene-carboxylic acid  
N,N-diisopropyl-5 $\alpha$ -androst-3-ene-17 $\beta$ -carboxamide-3-carboxylic acid;  
N,N-diisopropyl-androst-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid;  
30 17 $\beta$ -(N,N-diisopropylcarboxamide)-4-fluoro-5 $\alpha$ -androst-3-ene-3-carboxylic acid;

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- 17B-(N,N-Diisopropylcarboxamide)-androst-3,5,11-triene-3-carboxylic acid;
- 17B-(N,N-Diisopropylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid;
- 5 17B-(N-t-Butylcarboxamide)-androst-3,5,11-triene-3-carboxylic acid;
- 17B-(N-t-Butylcarboxamide)-androst-3,5-diene-3-thiocarboxylic acid,
- 10 N-t-butyl-androst-3,5-diene-17B-carboxamide-3-carboxylic acid,
- N,N-diisopropyl-androst-3,5-diene-17B-carboxamide-3-carboxylic acid,
- 20- $\alpha$ -(hydroxymethyl)-3- $\alpha$ -pregn-3-ene-3-carboxylic acid,
- 15 20- $\alpha$ -(hydroxymethyl)-4-fluoro-5- $\alpha$ -pregn-3-ene-3-carboxylic acid,
- 3-carbomethoxy-N,N-diisopropyl-androst-3, 5-diene-17 $\beta$ -carboxamide,
- 17 $\beta$ -N,N-diisopropylcarboxamide-5- $\alpha$ -androst-1,3-diene-3-carboxylic acid,
- 20 N,N-Diisopropyl 5- $\alpha$ -androst-2-ene-17 $\beta$ -carboxamide-3-carboxylic acid,
- N,N-diisopropyl androst-2-4-diene-17 $\beta$ -carboxamide-3-carboxylic acid,
- 25 N,N-diisopropyl 5- $\alpha$ -androstane-17 $\beta$ -carboxamide-3 $\beta$ -carboxylic acid,
- N,N-diisopropyl estr-3,5(10)-diene-17 $\beta$ -carboxamide-3-carboxylic acid,
- N,N-diisopropyl estr-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,
- 30 N-t-butyl-androst-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,

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- N,N-diisopropyl-androst-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
20- $\alpha$ -(hydroxymethyl)4-fluoro-5- $\alpha$ -pregn-3-ene-3-carboxylic acid,  
N,N-diisopropyl-5- $\alpha$ -androst-3-ene-17 $\beta$ -carboxamide-3-carboxylic acid,  
5 17 $\beta$ -(N,N-diisopropylcarboxamide)-4-fluoro-5- $\alpha$ -androst-3-ene-3-carboxylic acid,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-4-fluoro-androst-3,5-diene-3-carboxylic acid,  
10 3-carbomethoxy-N,N-diisopropyl-androst-3,5-diene-17 $\beta$ -carboxamide,  
17 $\beta$ -N,N-diisopropylcarboxamide-5- $\alpha$ -androst-1,3-diene-3-carboxylic acid,  
N,N-Diisopropyl-5- $\alpha$ -androst-2-ene-17 $\beta$ -carboxamide-3-carboxylic acid.  
15 N,N-diisopropyl androst-2,4-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
N,N-diisopropyl 5- $\alpha$ -androstane-17 $\beta$ -carboxamide-3 $\beta$ -carboxylic acid,  
20 N,N-diisopropyl estr-3,5(10)-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
N,N-diisopropyl estr-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-11-triene-3-carboxylic acid,  
25 17 $\beta$ -(N-t-butylcarboxamide)-androst-3,5-diene-3-thio-carboxylic acid,  
N-t-Butyl-5- $\alpha$ -androst-3-ene-17 $\beta$ -carboxamide-3-carboxylic acid,  
30 17 $\beta$ -(N-t-Butylcarboxamide)-6-fluoro-5- $\alpha$ -androst-3-ene-3-carboxylic acid,

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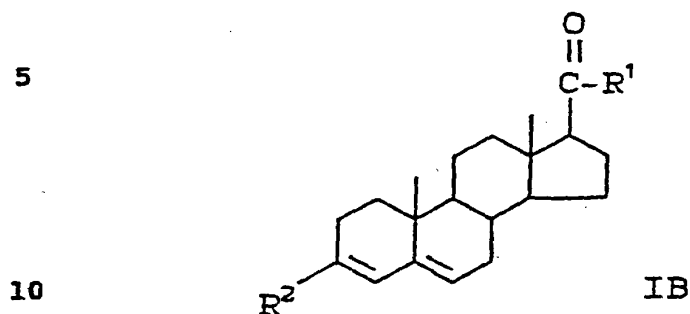
- 17B-(N-t-Butylcarboxamide)-6-fluoro-androst-3,5-diene-  
-3-carboxylic acid,  
3-Carbomethoxy-N-t-butyl-androst-3,5-diene-17B-carbox-  
amide,  
17B-N-t-Butylcarboxamide-5- $\alpha$ -androst-1,3-diene-3-car-  
boxylic acid  
5 N-t-Butyl-5- $\alpha$ -androst-2-ene-17B-carboxamide-3-carbox-  
ylic acid  
N-t-Butyl-androst-2,4-diene-17B-carboxamide-3-carbox-  
ylic acid,  
10 N-t-Butyl-5- $\alpha$ -androstane-17B-carboxamide-3-carboxylic  
acid, and  
20- $\alpha$ -(hydroxymethyl)-A-nor-5- $\alpha$ -pregn-1-ene-2-  
carboxylic acid,  
17B-(N-t-butylcarboxamide)-androst-3,5,11-triene-3-  
carboxylic acid,  
15 17B-(N-t-butylcarboxamide)-androst-3,5-diene-3-thio-  
carboxylic acid,  
N-t-Butyl-5- $\alpha$ -androst-3-ene-17B-carboxamide-3-  
carboxylic acid,  
20 17B-(N-t-Butylcarboxamide)-6-fluoro-5- $\alpha$ -androst-3-  
ene-3-carboxylic acid  
17B-(N-t-Butylcarboxamide)-6-fluoro-androst-3,5-  
diene-3-carboxylic acid,  
3-Carbomethoxy-N-t-butyl-androst-3,5-diene-17B-  
carboxamide,  
25 17B-N-t-Butylcarboxamide-5- $\alpha$ -androst-1,3-diene-3-  
carboxylic acid,  
N-t-Butyl-5- $\alpha$ -androst-2-ene-17B-carboxamide-3-  
carboxylic acid,  
30 N-t-Butyl-androst-2,4-diene-17B-carboxamide-3-  
carboxylic acid,

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- N-t-Butyl-5- $\alpha$ -androstande-17 $\beta$ -carboxamide-3-carboxylic acid,  
N-t-Butyl-estr-3,5(10)-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
N-t-Butyl-estr-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
5 N-t-Butyl-estr-3,5(10)-diene-17 $\beta$ -carboxamide acid-3-carboxylic acid,  
N-t-Butyl-estr-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid,  
10 20- $\alpha$ -(t-butylldimethylsiloxyethyl)-3-(trifluoromethylsulfonate)-5- $\alpha$ -pregn-3-ene,  
17 $\beta$ -(t-butylldimethylsilyloxyethyl)-3-(trifluoromethylsulfonate)-5- $\alpha$ -androstande-3-ene,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-androstande-3,5-diene,  
15 17 $\beta$ -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-4-fluoro-5- $\alpha$ -androstande-1,3-diene,  
20- $\alpha$ -(t-butylldimethylsiloxyethyl)-4-fluoro-3-(trifluoromethylsulfonate)-5- $\alpha$ -pregn-1,3-diene,  
20 17 $\beta$ -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-5- $\alpha$ -androstande-1,3 diene,  
17 $\beta$ -(N-t-butylcarboxamide)-3-(trifluoromethylsulfonate)-androstande-3,5-diene,  
17 $\beta$ -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-5- $\alpha$ -androstande-2-ene,  
25 17 $\beta$ -(N,N-diisopropylcarboxamide)-3-(trifluoromethylsulfonate)-androstande-2,4-diene,  
N-t-butyl-androstande-3,5-diene-3-bromo-17 $\beta$ -carboxamide, and  
30 N,N-diisopropyl-androstande-3,5-diene-3-bromo-17 $\beta$ -carboxamide.

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Also provided are 17 $\beta$ -acyl 3-carboxy-androst-3,5-diene of the formula:



wherein R<sup>1</sup> is (a) C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl;  
C<sub>3</sub>-C<sub>12</sub> cycloalkyl, which can be  
substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy  
or C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl;  
C<sub>6</sub>-C<sub>12</sub> aryl, or C<sub>7</sub>-C<sub>13</sub> aralkyl  
which can be substituted with one  
or more of: -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>  
COOH, including protected -OH,  
where m is 1-4, n is 1-3;

(b) C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl;  
C<sub>3</sub>-C<sub>12</sub> cycloalkyl, which can be  
substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy  
or C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl;  
C<sub>6</sub>-C<sub>12</sub> aryl, or C<sub>7</sub>-C<sub>13</sub> aralkyl  
which can be substituted with one  
or more of: -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl,  
C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>  
COOH, including protected -OH,  
where m is 1-4, n is 1-3, and

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$R^2$  is selected from  $\text{COOH}$ ,  $\text{SO}_3\text{H}$ ,  
 $\text{PO}(\text{OH})_2$ ,  $\text{PH}(\text{O})\text{OH}$ .

Specifically provided is wherein  $R^1$  is  
t-butyl, cycloalkyl, phenyl, p-hydroxyphenyl,  
1-adamantyl, 2-adamantyl, NH-t-butyl, NH-isobutyl,  
5 NH-cyclohexyl, NH-phenyl, NH-p-hydroxy-phenyl,  
NH-1-adamantyl, NH-2-adamantyl, and  $R^2$  is  $\text{COOH}$ ,

Representative compounds include:

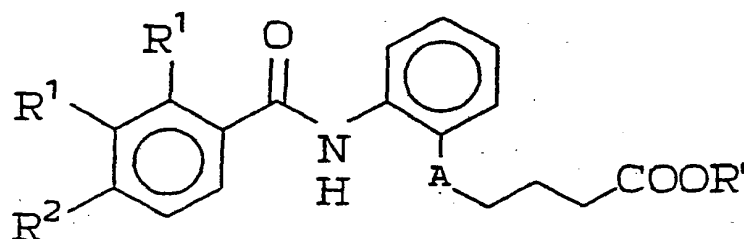
- 10 17B-(4-hydroxyphenylcarbonyl)-androsta-3,5-diene-3-  
carboxylic acid;  
17B-benzoyl-androsta-3,5-diene-3-carboxylic acid;  
17B-cyclohexylcarbonyl-androsta-3,5-diene-3-carboxy-  
15 lic acid;  
17B-isobutylcarbonyl-androsta-3,5-diene-3-carboxylic  
acid;  
17B-(4-hydroxymethylphenylcarbonyl)-androsta-3,5-  
diene-3-carboxylic acid;  
20 17B-(2-hydroxyethylphenylcarbonyl)-androsta-3,5-  
diene-3-carboxylic acid;  
17B-(4-methoxyphenylcarbonyl)-androsta-3,5-diene-  
3-carboxylic acid;  
17B-(4-carboxymethylphenylcarbonyl)-androsta-3,5-  
25 diene-3-carboxylic acid;  
N-t-butyl-androst-3,5-diene-17B-carboxamide-3-  
carboxylic acid;  
N-phenyl androst-3,5-diene-17B-carboxamide-3-  
carboxylic acid;  
30 N-1-adamantyl androst-3,5-diene-17B-carboxamide  
3-carboxylic acid;

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N-2-adamantyl androst-3,5-diene-17 $\beta$ -carboxamide  
3-carboxylic acid;

Also included and known in the art are  
non-steroidal 5 $\alpha$ -reductase inhibitors as developed by  
ONO Pharmaceutical Co., LTD., Osaka, Japan and  
as described in US patents 4,780,469; 4,847,275;  
4,939,141 and EPO Publication Nos. 0 173 516 and EPO  
0 291 245, and USP 4,980,372; and EPO Publn. 291,247  
and USP 5,037,852 disclosing certain novel fused  
benz(thio)amides and benzylaminophenylbutanoic  
derivatives, respectively.

The benzoylaminophenoxy butanoic acid derivatives  
are of the formula:

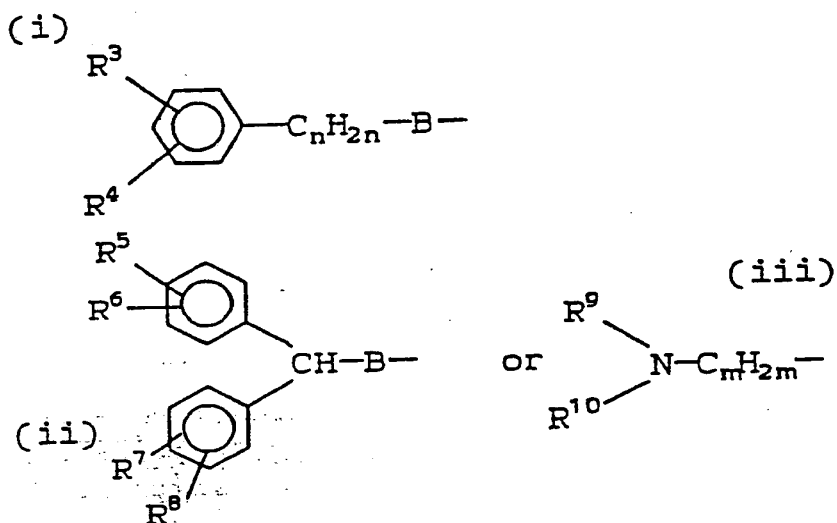


wherein R' is hydrogen or alkyl of from 1 to 4 carbon  
atom(s); A is oxygen atom, sulfur atom or sulfinyl  
(SO) group; both R<sup>1</sup>'s are methyl or chlorine, or the  
two R<sup>1</sup>'s and the carbon atoms of the benzene ring to  
which the two R<sup>1</sup>'s are linked together are  
cyclopentane, cyclohexane or a benzene ring; and



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$R^2$  represents a group of formula:



wherein B is oxygen, sulfur or a group of formula:  $NR^{11}$  wherein  $R^{11}$  is hydrogen or alkyl of from 1 to 4 carbon atom(s).

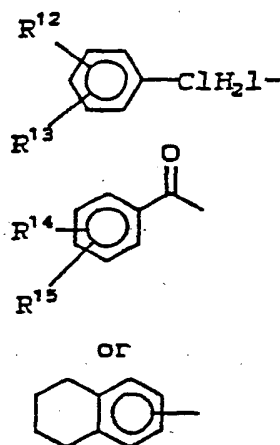
$R^3$ ,  $R^4$ ,  $R^5$ ,  $R^6$ ,  $R^7$ , and  $R^8$  are, independently, hydrogen, alkyl of from 1 to 4 carbon atom(s), halogen, trifluoromethyl or cyclobutylmethyl,

m is 0 or 1,

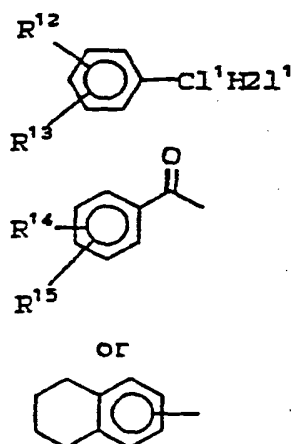
n is an integer of from 1 to 5, and

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$R^9$  is a hydrogen, alkyl of from 1 to 5 carbon atom(s) or a group of formula:



15 wherein  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  are,  
independently, hydrogen, alkyl of from 1 to  
4 carbon atom(s), halogen, trifluoromethyl  
or cyclobutylmethyl, and  $l$  is an integer of  
from 1 to 4, and  
20  $R^{10}$  is a group of formula:



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wherein R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are, independently, hydrogen, alkyl of from 1 to 4 carbon atom(s), halogen, trifluoromethyl or cyclobutylmethyl, and 1' is an integer of from 1 to 4; or non-toxic salts thereof.

5

Representative examples of each of these two classes of compounds whose synthesis and properties are disclosed in the above cited US issued patents include the following:

10

4-[2-(4-benzyloxy-2,3-dimethylbenzoylamino)phenoxy]butanoic acid;

4-[2-[4-(2-methylbenzyloxy)-2,3-dimethylbenzoylamino]butanoic acid;

15

4-[2-[4-(3-methylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

4-[2-[4-(4-methylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

20

4-[2-[4-(2,6-dimethylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

4-[2-[4-(4-ethylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

25

4-[2-[4-(4-isopropylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

30

4-[2-[4-(4-chlorobenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

4-[2-[4-(4-cyclobutylmethylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid;

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- 4-[2-[4-(2-phenylethoxy)-2,3-dimethylbenzoylamino]  
phenoxy]butanoic acid;
- 4-[2-[4-(3-phenylpropoxy)-2,3-dimethylbenzoylamino]  
phenoxy]butanoic acid;
- 5 4-[2-[4-(4-phenylbutoxy)-2,3-dimethylbenzoylamino]  
phenoxy]butanoic acid;
- 4-[2-[4-(5-phenylpentyloxy)-2,3-dimethylbenzoylamino]  
phenoxy]butanoic acid;
- 4-[2-[4-(1-(4-isobutylphenyl)ethoxy)-2,3-dimethyl-  
benzoylamino]phenoxy]butanoic acid;
- 10 4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]  
phenylthio]butanoic acid;
- 4-[2-[1-(4-isobutylphenyl)ethoxy)-2,3-dimethylbenzoyl  
amino]phenylthio]butanoic acid;
- 4-[2-[4-(4-propylbenzyloxy)-2,3-dimethylbenzoylamino]  
phenylsulfinyl]butanoic acid;
- 15 4-[2-[4-[N-(4-trifluoromethylphenylmethyl)amino]-  
2,3-dimethylbenzoylamino]phenoxy]butanoic acid;
- 4-[2-[4-(4-isobutylbenzyloxy)-5,6,7,8-tetrahydro  
naphthalene-1-carbonylamino]phenoxy]butanoic acid;
- 20 4-[2-[4-(4-isobutylbenzyloxy)naphthalene-1-carbonyl-  
amino]phenoxy]butanoic acid;
- 4-[2-[8-(4-isobutylbenzyloxy)-5,6,7,8-tetrahydro-  
naphthalene-1-carbonylamino]phenylthio]butanoic  
acid;
- 25 4-[2-[4-[bis(4-propylphenyl)methoxy]2,3-dimethyl-  
benzoylamino]phenoxy]butanoic acid;
- 4-[2-(4-diphenylmethoxy)-2,3-dimethylbenzoylamino]  
phenoxy]butanoic acid;
- 4-[2-[4-[bis(4-propylphenyl)methylamino]-2,3-  
dimethylbenzoylamino]phenoxy]butanoic acid;
- 30

- 4-[2-[4-[bis-(4-propylphenyl)methylthio]-2,3-  
dimethylbenzoylamino]phenoxy]butanoic acid;  
4-[2-[4-[N,N-bis(4-propylphenylmethyl)amino]-2,3-  
dimethylbenzoylamino]phenoxy]butanoic acid;  
4-[2-[4-[N,N-bis(4-trifluoromethylphenylmethyl)amino]-  
2,3-dimethylbenzoylamino]phenoxy]butanoic acid;  
5 4-[2-[4-N-methyl-N-(5,6,7,8-tetrahydronaphth-1-yl]  
aminomethyl]-2,3-dimethylbenzoylamino]phenoxy]-  
butanoic acid;  
8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
10 benzodioxane;  
8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-6 chloro-  
1,4-benzodioxane;  
8-(m-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
15 8-(o-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
8-(p-butylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
20 benzodioxane;  
8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
25 8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
8-(p-decylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane;  
8-(p-undecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-  
30 benzodioxane;

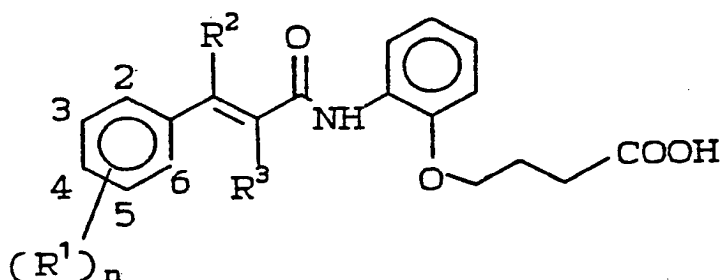
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- 8-(p-dodecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 5 8-(m-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(o-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-butyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 10 8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-propoxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 15 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 20 8-(o-decyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isopentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isohexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 25 8-[p-(1-methylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(N-methyl-N-(p-octynyloxy)benzoyl)]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 30 8-(p-oxyloxybenzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof;

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8-(p-isoheptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;  
 8-(p-isooctyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;  
 8-[p-(3,7-dimethyloctyloxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;  
 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;  
 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-7-carboxylic acid and methyl ester thereof, and the like.

Also included as a 5 $\alpha$ -reductase inhibitor in this invention is a cinnamoylamide of the following formula:



wherein R<sup>2</sup> and R<sup>3</sup> each independently represents a hydrogen or methyl group with the proviso that

- (i) when R<sup>2</sup> represents a methyl group, R<sup>3</sup> represents hydrogen and (R<sup>1</sup>)<sub>n</sub> represents a member selected from the group consisting of 3-group, 4-pentyl group, 4-neopentyl group, 4-(2-ethylbutyl) group and 4-(2-methylpentyl) group, or

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(ii) when  $R^2$  represents hydrogen,  $R^3$  represents a methyl group and  $(R^1)_n$  represents a 3-pentyl group, or non-toxic salts thereof.

Representative compounds include:

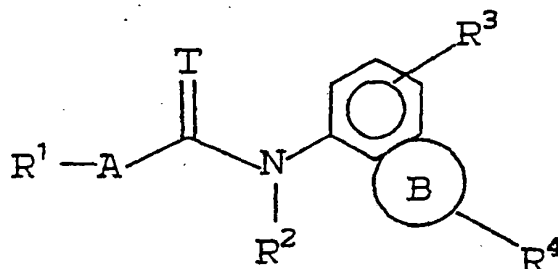
- 5 4-[2-(4-butylthio- $\beta$ -methylcinnamoylamino)phenoxy]  
butanoic acid  
4-[2-(4-cyclobutylmethyl) $\beta$ -methylcinnamoylamino)  
phenoxy]butanoic acid  
10 4-[2-(4-cyclohexylmethyl) $\beta$ -methylcinnamoylamino)  
phenoxy]butanoic acid  
4-[2-(4-{4-phenylbutyl})- $\beta$ -methylcinnamoylamino)  
phenoxy]butanoic acid  
4-[2-(4-phenoxy- $\beta$ -methylcinnamoylamino)phenoxy]  
15 butanoic acid  
4-[2-(3-pentyl- $\alpha$ -methylcinnamoylamino)phenoxy]  
butanoic acid  
4-[2-(4-phenethyl- $\alpha$ -methylcinnamoylamino)phenoxy]  
butanoic acid  
20 4-[2-(3-pentyl- $\beta$ -methylcinnamoylamino)phenoxy]  
butanoic acid  
4-[2-(4-neopentyl)- $\beta$ -methylcinnamoylamino)phenoxy]  
butanoic acid  
4-[2-{4-(2-ethylbutyl)- $\beta$ -methylcinnamoylamino)phenoxy]  
25 butanoic acid,  
4-[2-{4-(2-methylpentyl)- $\beta$ -methylcinnamoylamino)  
phenoxy]butanoic acid, and  
4-[2-(2-fluoro-4-pentyloxy- $\beta$ -methylcinnamoylamino)  
phenoxy]butanoic acid.

30



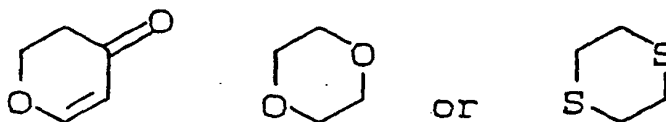
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Also included in this invention are fused benz(thio) amides of the formula:



wherein A represents a single bond or a group of methylene, ethylene, trimethylene, tetramethylene, vinylene, propenylene, butenylene, butadienylene or ethynylene group optionally being substituted by one, two or three of straight or branched alkyl group(s) of from 1 to 10 carbon atom(s) and/or phenyl group(s);

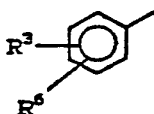
B represents a heterocyclic ring of from 4 to 8 members containing one, two or three hetero atom(s) selected from the group consisting of oxygen, nitrogen and sulphur atom(s), wherein the said ring may optionally be substituted by group(s) selected from oxo, thioxo and/or hydroxy group(s) including a ring of formula:



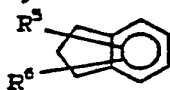
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T represents an oxygen atom or a sulphur atom;  
 $R^1$  represents a group of general formula:

(i)



(iii)



or

(ii)



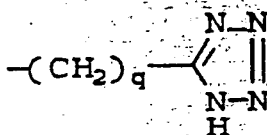
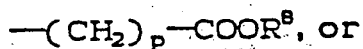
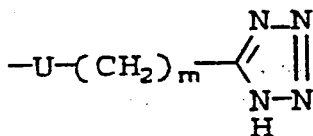
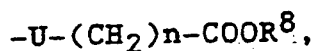
(iv) a straight or branched alkyl, alkenyl or alkynyl group of from 1 to 20 carbon atom(s), wherein  $R^5$  and  $R^6$  independently represent a hydrogen atom or a halogen atom or a straight or branched alkyl, alkenyl or alkynyl group of from 1 to 20 carbon atom(s) being unreplaced or replaced by one, two, three, four or five optional carbon atom(s), by oxygen atom(s), sulphur atom(s), halogen atom(s), nitrogen atom(s), benzene ring(s), thiophene ring(s), naphthalene ring(s), carbocyclic ring(s) of from 4 to 7 carbon atom(s), carbonyl group(s), carbonyloxy group(s), hydroxy group(s), carboxy group(s), azido group(s) and/or nitro group(s);

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$R^2$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s);

$R^3$  represents a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a group of general formula:  $--COOR^7$ , wherein  $R^7$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), or a straight or branched alkyl, alkoxy or alkylthio group of from 1 to 6 carbon atom(s);

$R^4$  represents a group of general formula:



wherein U represents an oxygen atom or a sulphur atom,  $R^8$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), n and m represent an integer of from 1 to 10, respectively, p and q represent zero or an integer of from 1 to 10, respectively, or non-toxic salts thereof.

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Representative compounds include:

- 7-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,  
7-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,  
7-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)benzo-  
5 furan,  
7-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)benzofuran,  
7-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
benzofuran,  
7-[p-(2E,7,-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
10 benzofuran,  
7-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
benzofuran and  
7-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)benzofuran,  
7-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihy-  
15 dro-1-benzofuran,  
7-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihy-  
dro-1-benzofuran,  
7-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihy-  
dro-1-benzofuran,  
20 7-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-dihy-  
dro-1-benzofuran,  
7-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihy-  
dro-1-benzofuran,  
8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)  
25 quinoline,  
8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
quinoline,  
8-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
quinoline,  
30 8-[p-(2E,7-octadienyloxy)benzoyl]amino-4-hydroxy-  
quinoline-2-carboxylic acid,

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- 8-[p-(4-phenylbutoxy)benzoyl]amino-4-hydroxyquinoline-  
2-carboxylic acid,  
8-[p-[4-(2-thienyl)butoxy)benzoyl]amino-4-hydroxy-  
quinoline-2-carboxylic acid,  
8-[p-(2E,7-octadienyloxy)benzoyl]amino-4-hydroxy-  
2-(tetrazolyl)quinoline,  
5 8-[p-[4-(2-phenylbutoxy)benzoyl]amino-4-hydroxy-  
2-(5-tetrazolyl)quinoline and,  
8-(p-pentylcinnamoyl)amino-4-hydroxy-2-(5-tetrazolyl)  
quinoline and,  
10 4-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,3-ben-  
zodioxole,  
4-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,3-ben-  
zodioxole,  
4-[p-[4-(phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)  
1,3-benzodioxole,  
15 4-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,3-ben-  
zodioxole,  
9-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
3,4-dihydro-2H-1,5-benzodioxepin,  
20 9-[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetra-  
zolyl)-3,4-dihydro-2H-1,5-benzodioxepin,  
9-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)  
-3,4-dihydro-2H-1,5-benzodioxepin,  
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-2,3-  
25 dihydro-1,4-benzoxazine,  
8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
2,3-dihydro-1,4-benzoxazine and  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-  
dihydro-1,4-benzoxazine,  
30 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
4-oxo-4H-1-benzothiopyran,

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- 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
3,4-dihydro-2H-1-benzopyran,  
8-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
3,4-dihydro-2H-1-benzopyran,  
8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-  
5 1-benzopyran,  
8-(p-pentylbenzoyl)amino-4-oxo-4H-1-benzopyran-2-  
carboxylic acid and ethyl ester thereof,  
8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
10 8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran and  
8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
15 4H-1-benzopyran  
8-(p-butoxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
20 8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
25 4H-1-benzopyran,  
8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-  
4H-1-benzopyran,  
8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-6-fluoro-  
4-oxo-4H-1-benzopyran,  
30 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-6-methyl-  
4-oxo-4H-1-benzopyran and

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- 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran and  
8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8-(p-geranyloxybenzoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
5 8[p-(2E-nonyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(2E-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
10 8[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(2E-heptenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(2E-hexenyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
15 8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-fluoro-4-oxo-4H-1-benzopyran,  
8[p-(2E-octenyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,  
20 8[p-(2E,7-octadienyloxy)benzoyl]amino-2-(5-tetrazolyl)-6-chloro-4-oxo-4H-1-benzopyran,  
8[p-(2-octynyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran, thereof  
8[p-(4-chlorobutoxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
25 8[p-(5-chloropentyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
30 8[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,

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- 8[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
4-oxo-4H-1-benzopyran,  
8[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
6-methyl-4-oxo-4H-1-benzopyran,  
8[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
6-methyl-4-oxo-4H-1-benzopyran and  
5 8[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
4-oxo-4H-1-benzopyran,  
8[p-(3-phenylpropoxy)benzoyl]amino-2-(5-tetrazolyl)-  
4-oxo-4H-1-benzopyran,  
10 8[p-(3-phenyl-2E-propenyloxy)benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
4-oxo-4H-1-benzopyran,  
8[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
6-methyl-4-oxo-4H-1-benzopyran,  
15 8[p-[2-(2-naphthy)ethoxy]]benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-[2-(2-naphthyl)ethoxy]]benzoyl]amino-2-(5-  
tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,  
20 8[p-[3-(3,4-dichlorophenyl)propoxy]benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-[3-(3,4-dichlorophenyl)propoxy]benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-[3-(p-chlorophenyl)butoxy]benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,  
25 8[p-[3-(p-chlorophenyl)butoxy]benzoyl]amino-6-  
methyl-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-[3-(p-chlorophenyl)propoxy]benzoyl]amino-6-  
methyl-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
30 8[p-[4-(2-thienyl)butoxy]benzoyl]amino-2-(5-  
tetrazolyl)-4-oxo-4H-1-benzopyran,



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- 8[p-[4-(2-thienyl)butoxy]benzoyl]amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,  
8-(p-pentylcinnamoyl)amino-4-oxo-4H-1-benzopyran-2-carboxylic acid and methyl ester thereof,  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
5 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-methyl-4-oxo-4H-1-benzopyran,  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-fluoro-4-oxo-4H-1-benzopyran,  
10 8-(p-pentylcinnamoyl)amino-6-methyl-4-oxo-4H-1-benzopyran-2-carboxylic acid and ethyl ester thereof,  
8-(p-butylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
15 8-(p-hexylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8-(p-heptylcinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8-cinnamoylamino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
20 8-(p-hexyloxycinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8-(p-heptyloxycinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
25 8-(p-isohexyloxycinnamoyl)amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
8[p-(2-octynyloxy)cinnamoyl]amino-4-oxo-4H-1-benzopyran-2-carboxylic acid,  
8[p-(5-chloropentyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,  
30 8[p-(6-chlorohexyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-4-oxo-4H-1-benzopyran,

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- 8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-pentylbenzoyl)amino-2-(5-tetrazolyl)-6 chloro-1,4-benzodioxane;
- 5 8-(m-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(o-pentylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-butylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 10 8-(p-hexylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-heptylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 15 8-(p-nonylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-decylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 20 8-(p-undecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-dodecylbenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 25 8-(m-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(o-pentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 30 8-(p-butyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;

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- 8-(p-nonyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-propoxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-hexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 5 8-(p-heptyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 10 8-(o-decyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isopentyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isohexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 15 8-[p-(1-methylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(N-methyl-N-(p-octynyloxy)benzoyl)]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 20 8-(p-octyloxybenzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof;
- 8-(p-isohexyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-isooctyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 25 8-[p-(3,7-dimethyloctyloxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane;
- 8-(p-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-7-carboxylic acid,
- 30 8-[p-(2E-octyloxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

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- 8-[p-(3-butenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(3Z-hexenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2Z-octenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
5 8-[p-(2E-nonyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[N-methyl-N-[p-(2E-cctenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
10 8-[p-(2E-hexenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(3E-heptenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-octenyloxy)benzoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof,  
15 8-[p-(2E-heptenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(4-pentenylloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
20 8-[p-(2E-decenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-geranyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-  
8-[p-(2E,7-octadienyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
25 8-[p-(2E-pentenylloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-butenylloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
30 8-[p-(3E-octenyloxy)benzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

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- 8-[p-(7-octenyloxy)benzoyl]amino-2-(5-tetrazo-  
lyl)-1,4-benzodioxane,  
8-[p-(2E,4E-octadienyloxy)benzoyl]amino-2-(5-tetrazo-  
lyl)-1,4-benzodioxane and  
8-[p-(2E-octadienyloxy)benzoyl]amino-2-(5-tetrazo-  
5 ly1)-1,4-benzodioxane,  
8-[p-(2-octynyloxy)benzoyl]amino-2-(5-tetrazoly1)-  
1,4-benzodioxane,  
8-[p-(2-octynyloxy)benzoyl]amino-1,4-benzodioxane-2-  
carboxylic acid and methyl ester thereof and  
10 8-[p-(2-isooctynyloxy)benzoyl]amino-2-(5-tetrazoly1)-  
1,4-benzodioxane  
8-(p-pentylthiobenzoyl)amino-2-(5-tetrazoly1)-1,4-ben-  
zodioxane,  
8-(m-pentylthiobenzoyl)amino-2-(5-tetrazoly1)-1,4-ben-  
15 zodioxane  
8-(o-pentylthiobenzoyl)amino-2-(5-tetrazoly1)-1,4-ben-  
zodioxane and  
8-(p-heptylthiobenzoyl)amino-2-(5-tetrazoly1)-1,4-ben-  
zodioxane  
20 8-[p-(6-chlorohexyloxy)benzoyl]amino-2-(5-tetrazoly1)-  
1,4-benzodioxane,  
8-[p-(5-chloropentyloxy)benzoyl]amino-2-(5-tet-  
razoly1)-1,4-benzodioxane,  
8-[p-(4-chlorobutoxy)benzoyl]amino-2-(5-tetrazoly1)-  
25 1,4-benzodioxane,  
8-[p-(7-chloroheptyloxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,  
8-[p-(8-chlorooctyloxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,  
30 8-[p-(9-chlorononyloxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane and

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- 8-[p-(t-bromopentyloxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4,-benzodioxane-2-carboxylic acid and  
methyl ester thereof
- 8-[p-hexyloxymethyl)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane
- 5 8-[p-(cyclohexylmethoxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 8-[p-(4-cyclohexylbutoxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane, and
- 8-[p-(2-cyclohexylethoxy)benzoyl')amino-2-(5-tetra-  
10 zoly1)-1,4-benzodioxane, and
- 8-[p-(p-butylphenyl)methoxybenzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 8-[p-(5-phenylpentyloxy)benzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 15 8-[p-(3-phenylpropoxy)benzoyl')amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 8-[p-(p-propylphenyl)methoxybenzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 8-[p-(3-phenyl-2-propenyloxy)benzoyl]amino-2-(5-tetra-  
20 zoly1)-1,4-benzodioxane,
- 8-[p-(4-phenylbutoxy)benzoyl]amino-2-(5-tetrazoly1)-  
1,4-benzodioxane,
- 8-[p-(o-pentylphenyl)methoxybenzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 25 8-[p-(m-butylphenylmethoxybenzoyl]amino-2-(5-tetra-  
zoly1)-1,4-benzodioxane,
- 8-(p-phenylmethoxybenzoyl)amino-2-(5-tetrazoly1)-1,4-  
benzodioxane,
- 8-[p-(2-phenylethoxy)benzoyl')amino-2-(5-tetrazoly1)  
30 1,4-benzodioxane,

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- 8-[p-4-phenylbutoxy)benzoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
8-[p[-2-(2-naphthyl)ethoxy]benzoyl')amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-[p-[3-(p-chlorophenyl)propoxy]benzoyl]amino-2-(5-  
5 tetrazolyl)-1,4-benzodioxane and  
8-[p-[4-(p-chlorophenyl)butoxy]benzoyl]amino-2-(5-  
tetrazolyl)-1,4-benzodioxane,  
8-[p-(5-methoxycarbonylpentyloxy)benzoyl]amino-2-  
(5-tetrazolyl)-1,4-benzodioxane,  
10 8-[p-(6-acetyloxyhexyloxy)benzoyl]amino-2-(5-tetraz-  
olyl)-1,4-benzodioxane,  
8-[p-(6-hydroxyhexyloxy)benzoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-[p-(2E-octenoyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane and  
15 8-(p-octanoylbenzoyl)amino-2-(5-tetrazolyl)-1,4-ben-  
zodioxane  
8-[p-(3-phenylthiopropoxy)benzoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
20 8-[p-(3-phenoxypropoxy)benzoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
8-[p-(2-phenylthioethoxy)benzoyl')amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane and  
8-[p-(2-phenoxyethoxy)benzoyl')amino-2-(5-tetrazolyl)-  
25 1,4-benzodioxane  
8-[p-[2-(3-thienyl)ethoxy]benzoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane and  
8-[p-[4-(2-thienyl)butoxy]benzoyl')amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane  
30 8-[p-(5-azidopenyloxy)benzoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,

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- 8-[p-(5-dimethylaminopentyloxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(4-nitrobutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
5 8-[p-(2-azidoethoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(4-azidobutoxy)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2-octenoylamino)benzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
10 8-(p-pentyloxy-m-methoxybenzoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-octenyloxy)-m-chlorobenzoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane  
8-(2-naphthylcarbonyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
15 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentylcinnamoyl)amino-1,4-benzodioxane-2-carboxylic acid and methyl ester thereof,  
20 8-(p-heptylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[N-methyl-[N-(pentylcinnamoyl)]amino]-2-(5-tetrazolyl)-1,4-benzodioxane,  
5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-7-chloro-1,4-benzodioxane,  
25 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-chloro-1,4-benzodioxane,  
8-(p-ethylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
30 8-(p-propylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,



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- 8-(p-butylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-6-methyl-1,4-benzodioxane,  
8-(o-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
5 8-(m-octylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-5-carboxylic acid and methyl ester thereof,  
10 5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-8-carboxylic acid and methyl ester thereof,  
8-(p-hexylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
15 8-(p-nonylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-6-carboxylic acid and methyl ester thereof,  
20 5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane-7-carboxylic acid and methyl ester thereof,  
8-(p-octylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
25 8-(p-decylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-P-isopropylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
30 8-(p-isobutylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

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- 8-(p-isopentylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentyl-2-methylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-pentyl-3-methylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane and  
5 8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)methyl-1,4-benzodioxane  
8-(p-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
10 8-(m-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(o-pentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-propoxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
15 8-(p-butoxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-octyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
20 8-(p-hexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-heptyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-isopentyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
25 8-(p-iso-hexyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(1-methylbutoxy)-cinnamoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
30 8-(p-iso-heptyloxy-cinnamoyl)amino-2-(5-tetrazolyl)-1,4-benzodioxane,

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- 8-(p-isooctyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-(p-isohexyloxy-2-methylcinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane and  
8-(p-isohexyloxy-2-phenylcinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
5 8-[p-(2E-octenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2-propenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
10 8-[p-(3-butenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(3Z-hexenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-2Z-pentyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
15 8-[p-(2E-nonyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(3E-heptenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
20 8-[p-(2E-heptenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-hexenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-pentyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
25 8-[p-(4-pentyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane,  
8-[p-(2E-butenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane and  
30 8-[p-(2E-decenyloxy)cinnaoyl]amino-2-(5-tetrazolyl)-1,4-benzodioxane

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- 8-[p-(2-octynyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane and  
8-[p-(2-pentynyloxy)cinnamoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
5 8-(p-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
8-(m-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane and  
8-(o-pentylthiocinnamoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
10 8-[p-(6-chlorohexyloxy)cinnamoyl]amino-2-(5-tetra-  
zolyl)1,4-benzodioxane,  
8-[p-(4-chlorobutoxy)cinnamoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
8-[p-(5-chloropentyloxy)cinnamoyl]amino-2-(5-tetra-  
15 zolyl)-1,4-benzodioxane and  
8-[p-(7-chloroheptyloxy)cinnamoyl')amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane  
8-(p-isopentyloxymethyl-cinnamoyl)amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
20 8-(p-cyclohexylcinnamoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
8-(p-cyclohexylmethoxycinnamoyl)amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-[p-(4-cyclohexylbutoxy)cinnamoyl')amino-2-(5-tetra-  
25 zolyl)-1,4-benzodioxane and  
8-[p-(2-cyclohexylethoxy)cinnamoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-(p-phenylmethylcinnamoyl)amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
30 8-(p-phenylmethoxycinnamoyl)amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,

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- 8-[p-(2-phenylethoxy)cinnamoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
8-[p-(4-phenylbutoxy)cinnamoyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane,  
8-[p-(5-phenylpentyloxy)cinnamoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane and  
8-[p-(3-phenylpropoxy)cinnamoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-[p-(6-acetyloxyhexyloxy)cinnamoyl]amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane,  
8-[p-[2-(2-thienyl)ethoxy]-cinnamoyl]-amino-2-(5-  
tetrazolyl)-1,4-benzodioxane,  
8-(m,p-dimethoxycinnamoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
8-(m-methoxy-p-pentyloxycinnamoyl)amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane and  
8-(p-pentyloxy-m-chlorocinnamoyl)amino-2-(5-tetra-  
zolyl)-1,4-benzodioxane  
8-[3-(5-indanyl)acryloyl]amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
N-(2-hexadecenoyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
8-(p-pentylphenylacetyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane and  
8-[3-(p-pentylphenyl)propionyl]amino-2-(5-tetrazolyl)-  
1,4-benzodioxane  
8-(p-hexylphenylpropioloyl)amino-2-(5-tetrazolyl)-1,4-  
benzodioxane,  
8-[5-(p-propoxyphenyl)penta-2E,4E-dienoyl]amino-2-  
(5-tetrazolyl)-1,4-benzodioxane and  
8-[5-(p-butylphenyl)penta-2E,4E-dienoyl]amino-2-(5-  
tetrazolyl)-1,4-benzodioxane,

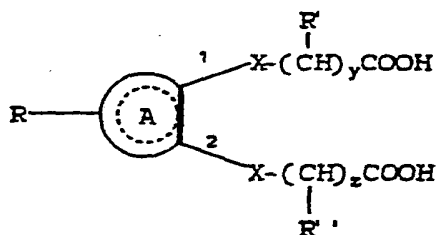
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8-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-dithianaphthalene and  
 5-(p-pentylcinnamoyl)amino-2-(5-tetrazolyl)-2,3-dihydro-1,4-dithianaphthalene and sodium salts thereof.

5

Also included are aromatic 1,2-di(thio)ethers of the formula:

10



15

20

wherein

A is an 1,2-disubstituted aromatic ring; preferably a benzene ring;

wherein

25

X is independently O, S, SO, or SO<sub>2</sub>;

R is H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

phenyl or substituted phenyl,

halo,

30

haloalkyl,

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hydroxy,  
carboxy,  
cyano,  
C<sub>1</sub>-C<sub>4</sub> alkoxy,  
C<sub>1</sub>-C<sub>4</sub> alkylthio,  
5 C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,  
C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl,  
nitro,  
amino,  
C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;

10

R' and R'' are independently

H,  
halo,  
C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,  
15 amino, or oxo, where CH-R' or CH-R''  
in the formula become -C=O;

y is 1-6;

20

z is 6-20; and

wherein

R'  
|  
(CH)<sub>y</sub> and

25

R''  
|  
(CH)<sub>z</sub> can independently represent substituted  
or unsubstituted alkyl radicals or alkenyl  
radicals containing at least one alkene bond;  
and pharmaceutically acceptable salts and esters  
thereof.

30

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The compounds of the instant invention are inhibitors of the human testosterone-5 $\alpha$ -reductase enzyme.

The scope of the compounds of the instant invention are described by the above-described  
5 formula.

In the description of the formula the following terms are used which are hereby defined:

10 X in the general formula above is O or S, preferably where one X is O, and particularly where both Xs are O, e.g., resulting in the catechol structure.

"C<sub>1</sub>-C<sub>4</sub> alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl,  
15 cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl.

"C<sub>1</sub>-C<sub>4</sub> alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

20 "Halo" includes fluoro, chloro, bromo or iodo.

"Substituted phenyl" includes phenyl substituted by one or more of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halo, and the like, as defined above. representative examples include o, m-, p-methoxy  
25 phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

"Haloalkyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with one or more "halo" as  
30 defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.



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"C<sub>1</sub>-C<sub>4</sub> alkylthio" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.

5 "C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

10 "C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one sulfonyl group, -SO<sub>2</sub>-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like.

15 "C<sub>1</sub>-C<sub>4</sub> mono or dialkyl amino" includes amino, substituted with one or more C<sub>1</sub>-C<sub>4</sub> alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, N,N-dimethylamino, N,N-diethylamino, methyl-t-butylamino, and the like.

20 The R group or groups on the benzene ring can be present initially in the process, such as in starting material I in Flow Chart A, e.g. phenyl, methyl, methoxy, cyano, trifluoromethyl, carbomethoxy, or added later by a conventional reaction, e.g. chloro, as by chlorination, nitro by  
25 nitration, or created from a starting or added functional group present, e.g. converting a nitro to an amino group by catalytic reduction, then alkylating to a mono or dialkylamine. An amino group can be subjected to diazotization to a hydroxy group,

30

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which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J. Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be alkylated to alkylthio, which can be oxidized to the corresponding sulfoxide or sulfone. Preferred substituents are H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant, salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, acetate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

$$\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$$
 where y is 1-6, preferably 3, can contain at least one R' substituent as defined above, and can be, e.g., -CH<sub>2</sub>-; -CH<sub>2</sub>-CH<sub>2</sub>-; -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-,  
 -CH-; -CH-CH<sub>2</sub>-; -CH<sub>2</sub>-CH-; -CH<sub>2</sub>-CH-CH<sub>2</sub>-; -CH<sub>2</sub>-CH-CH<sub>2</sub>-;  
 $\begin{array}{ccccccc} \text{CH}_3 & \text{CH}_3 & \text{Cl} & \text{OCH}_3 & \text{OCH}_2\text{CH}_3 \end{array}$   
 and the like.

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An alkene bond can also be present in R'  
 $(CH)_y-$ , e.g.,  $CH_2-CH=CH-$ ;  $CH_2-CH=CH-CH_2-$ ;  
 $-CH_2-CH=CH-(CH_2)_2-$ ; and the like.

$(CH)_z$ , where z is 6-20, preferably 10-16, can  
 5 contain at least one R'' substituent as defined above,  
 and can be; e.g.,  $-(CH_2)_6-$ ,  $-(CH_2)_{20}-$ ,  $-(CH_2)_9-CH-$ ;  
 $CH_3$   
 $-CH_2-CH-(CH_2)_9-$ ;  $-(CH_2)_5-CH-(CH_2)_4-$ ;  
 $F$   $OCH_3$   
 10 and the like.

An alkene bond can also be present in  
 $(CH)_z$ , e.g.,  $CH_2-CH=CH-(CH_2)_8-$ ;  $-(CH_2)_8-CH=CH(CH_2)_2-$ ;  
 15  $-(CH_2)_9-CH=CH-(CH_2)_9-$ ;  $(CH_2)_4-CH=CH-(CH_2)_4-$ ; and the  
 like.

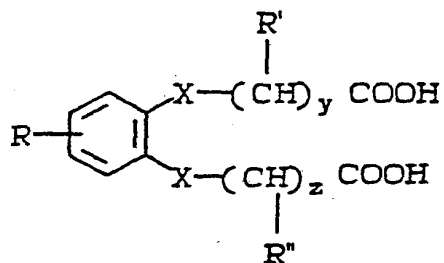
R' and R'' can also be  $-NHC(O)CH_3$ , which can  
 be hydrolyzed to amino by conventional acid or base  
 hydrolysis in the final molecule; R' and R'' can also  
 20 be oxo, obtained by, for example, HBr addition to an  
 alkene followed by conversion to an alcohol and  
 subsequent oxidation to the ketone.

Preferred is where one R' or R'' is H and  
 particularly preferred is where both  $(CH)_y$  and  $(CH)_z$   
 25 are alkyl.

Preferred compounds of the instant invention  
 are given by the following formulas;

30

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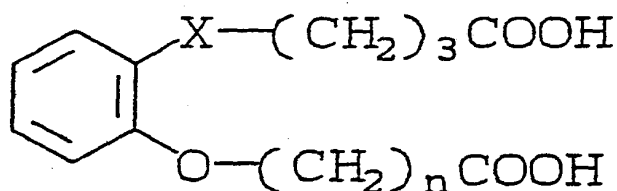


5

wherein

10 one X is O and R, R', R'', y and z are defined above;  
and particularly preferred are the compounds,

15



20

25

wherein

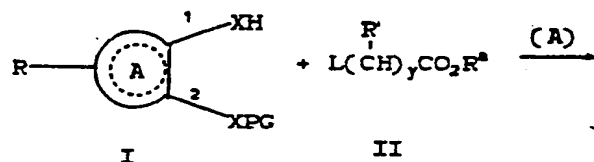
X is O or S and n is 10-16.

30 The compounds of the instant invention can  
be made by the procedure outlined in the following  
Flowchart A-1.

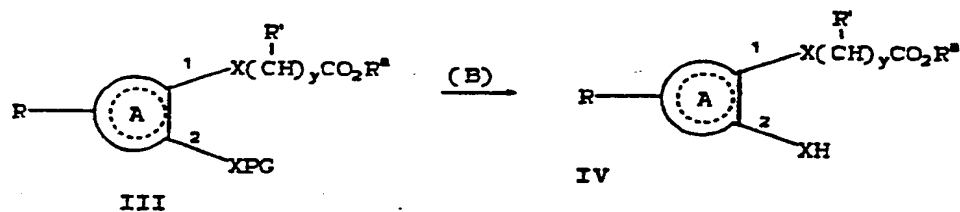
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## FLOW CHART A-1

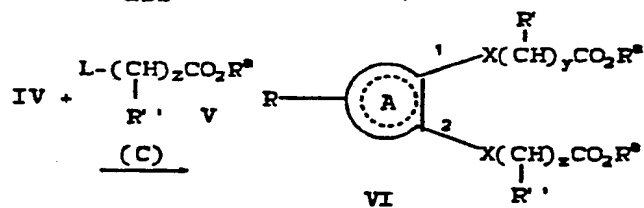
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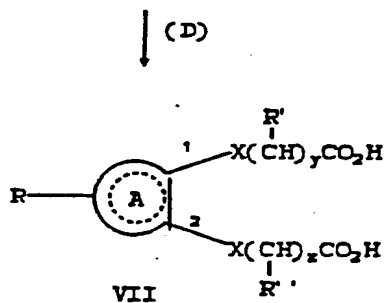
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As seen in Flow Chart A-1, Compound I is the starting substrate in the invention process and is a 1,2-substituted benzene ring. X can be independently O or S and "PG" represents a hydroxy or thio protecting group which is inactive during Step (A) but can be subsequently removed by, e.g. palladium on carbon catalyst in ethanol under a pressurized H<sub>2</sub> atmosphere.

Examples of "PG" protecting groups which are conventional and known in the art (See "Protective Groups in Organic Synthesis" by Theodora W. Greene - 1981 - John Wiley - Chapter 2, "Protection for the Hydroxyl Group, Including 1,2- and 1,3-Diols" pp. 16-87 and Chapter 6 "Protection for the Thiol Group" pp. 193-218).

Representative examples of "PG" include: benzyl, p-methoxybenzyl, p-halobenzyl; including p-chlorobenzyl, p-fluorobenzyl, and the like. Other protective groups which are known will be obvious to one skilled in the art to carry out the function of Step (A).

Representative examples of compounds useful as I in the instant invention, include, but are not limited to the following:

2-(benzyloxy)-phenol,  
2-benzyloxy-thiophenol,  
2-(benzylthio)-phenol,  
2-(benzylthio)thiophenol,  
3-methoxy-2-benzyloxyphenol,  
2-benzyloxy-4-methoxyphenol,  
3-methyl-2-benzyloxyphenol,  
2-benzyloxy-5-methylphenol,

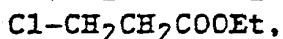
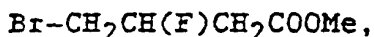
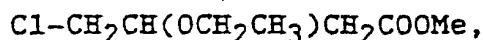
- 97 -

- 2-benzyloxy-4-methylphenol,  
2-benzyloxy-5-methylphenol,  
2-benzyloxy-3,5-diisopropylphenol,  
2-benzyloxy-3,5-di-t-butylphenol,  
2-benzyloxy-4-t-butylphenol,  
5 2-benzyloxy-3-ethylphenol,  
2-benzyloxy-5-phenylphenol,  
2-benzyloxy-4-methyl-1-thiophenol,  
2-benzyloxy-5-trifluoromethyl-1-thiophenol,  
2-benzyloxy-6-methoxy-1-thiophenol,  
10 2-benzylthio-4-methyl-thiophenol,  
2-benzylthio-5-methylsulfonyl-phenol, and the like.

Representative examples of II useful in  
the invention process where L is a leaving group,  
15 e.g., halogen, including bromo, chloro, or sulfonate,  
and the like, and R<sup>a</sup> is a C<sub>1</sub>-C<sub>4</sub> linear or branched  
alkyl portion of the ester, including methyl, ethyl,  
isopropyl, t-butyl, sec-butyl, and the like, and  
where R<sup>1</sup> and Y are or defined above, include, but  
20 are not limited to:

- Br-CH<sub>2</sub>-COOMe,  
Cl-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOCH<sub>2</sub>CH<sub>3</sub>,  
Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOMe,  
25 Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOEt,  
Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOCH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  
Br-(CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)COOMe,  
Br-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>COOEt,  
Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOMe,  
30 Br-CH<sub>2</sub>CH(OCH<sub>3</sub>)CH<sub>2</sub>COOCH(CH<sub>3</sub>)<sub>2</sub>,

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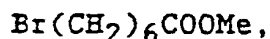
and the like.

5           In Step (A) the condensation of I and II  
to produce III takes place in an non-hydroxylated  
polar organic solvent, e.g., acetone, ethyl acetate,  
methylethylketone, dioxan, THF, diethylketone, and  
the like. A proton acceptor is also present, e.g.  
10   potassium carbonate, sodium bicarbonate, pyridine,  
triethylamine, and the like. Generally, the reac-  
tion is carried out under an inert atmosphere, e.g.  
dry nitrogen, and heated at reflux or allowed to sit  
for an extended period of time at room temperature.  
15   Workup is conventional.

          In Step (B) the protecting group, "PG",  
is catalytically removed at ambient temperature  
under a pressurized, hydrogen atmosphere in an  
organic solvent to produce IV, being a phenol or  
20   thiophenol. Operable catalysts include 5% Pd/C,  
and the like. The organic solvent should be inert  
under the reaction conditions and includes ethyl  
acetate, ethanol, methanol, dioxane, and the like.

          Step (C) involves reacting IV with V to  
25   produce VI, the diester. The reaction conditions  
are similar to those described in Step (A) utilizing  
an inert organic solvent for the reactants and a  
proton acceptor.

          Representative examples of V useful in the  
30   invention are:





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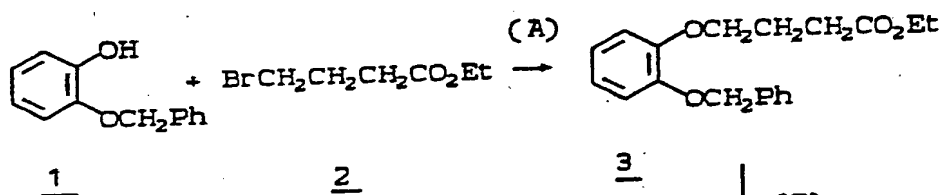
- $\text{Br}(\text{CH}_2)_7\text{COOMe},$   
 $\text{Br}(\text{CH}_2)_8\text{COOMe},$   
 $\text{Br}(\text{CH}_2)_9\text{COOMe},$   
 $\text{Br}(\text{CH}_2)_{10}\text{COOMe},$   
 $\text{Br}(\text{CH}_2)_{11}\text{COOMe},$   
5  $\text{Cl}(\text{CH}_2)_{12}\text{COOEt},$   
 $\text{Cl}(\text{CH}_2)_{13}\text{COOCH}(\text{CH}_3)_2,$   
 $\text{Cl}(\text{CH}_2)_{14}\text{COOCH}_2\text{CH}_2\text{CH}_3,$   
 $\text{Br}-(\text{CH}_2)_{15}\text{COOMe}$   
 $\text{Br}-(\text{CH}_2)_{16}\text{COOMe}$   
10  $\text{Br}(\text{CH}_2)_{16}\text{COOCH}_2\text{CH}_3,$   
 $\text{Br}(\text{CH}_2)_{17}\text{COOC}(\text{CH}_3)_3,$   
 $\text{Br}(\text{CH}_2)_{18}\text{COOMe},$   
 $\text{Br}(\text{CH}_2)_{19}\text{COOEt},$   
 $\text{Br}(\text{CH}_2)_{20}\text{COOMe},$   
15  $\text{Br}(\text{CH}_2)_2\text{CH}(\text{CH}_3)-(\text{CH}_2)_{10}\text{COOMe},$   
 $\text{Br}-\text{CH}_2\text{CH}(\text{CH}_3)(\text{CH}_2)_{10}\text{COOMe},$   
 $\text{Br}-\text{CH}_2\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{COOEt},$   
 $\text{Br}-\text{CH}_2\text{CH}(\text{OCH}_3)(\text{CH}_2)_7\text{COOCH}(\text{CH}_3)_2,$   
 $\text{Cl}-\text{CH}_2\text{CH}(\text{OCH}_2\text{CH}_3)\text{CH}_2\text{CH}_2\text{COOMe},$   
20  $\text{Br}-\text{CH}_2\text{CH}(\text{NHCOCCH}_3)-(\text{CH}_2)_{10}-\text{CH}_2-\text{COOMe},$   
 $\text{Cl}-\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-(\text{CH}_3)_{11}-\text{COOEt},$   
 $\text{Br}-\text{CH}_2-\text{CH}=\text{CH}(\text{CH}_2)_8-\text{COOEt},$   
 $\text{Br}-\text{CH}_2-\overset{\text{CH}_2}{\underset{\text{CH}_2}{\text{C}}}-(\text{CH}_2)_{10}\text{CH}_2\text{COOMe},$   
25  $\text{Br}-\text{CH}_2-(\text{CH}_2)_9-\text{CH}=\text{CH}-\text{COOMe},$   
and the like.

In Step (D), the diester can be deesterified  
 by aqueous basic hydrolysis, e.g. NaOH in MeOH/H<sub>2</sub>O  
 to yield the diacid VII upon acidification.

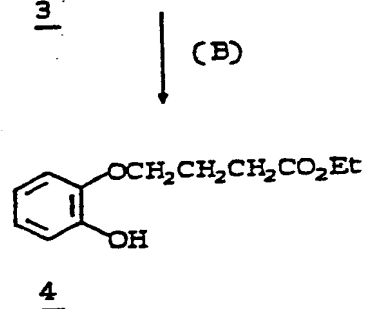
- 100 -

## FLOW CHART B-1

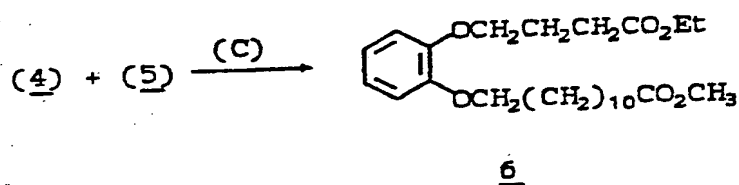
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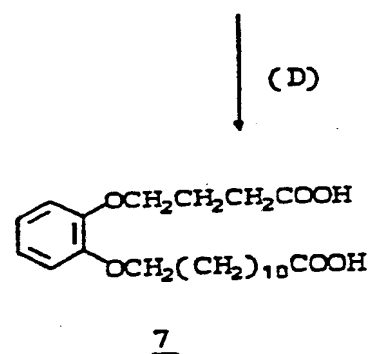
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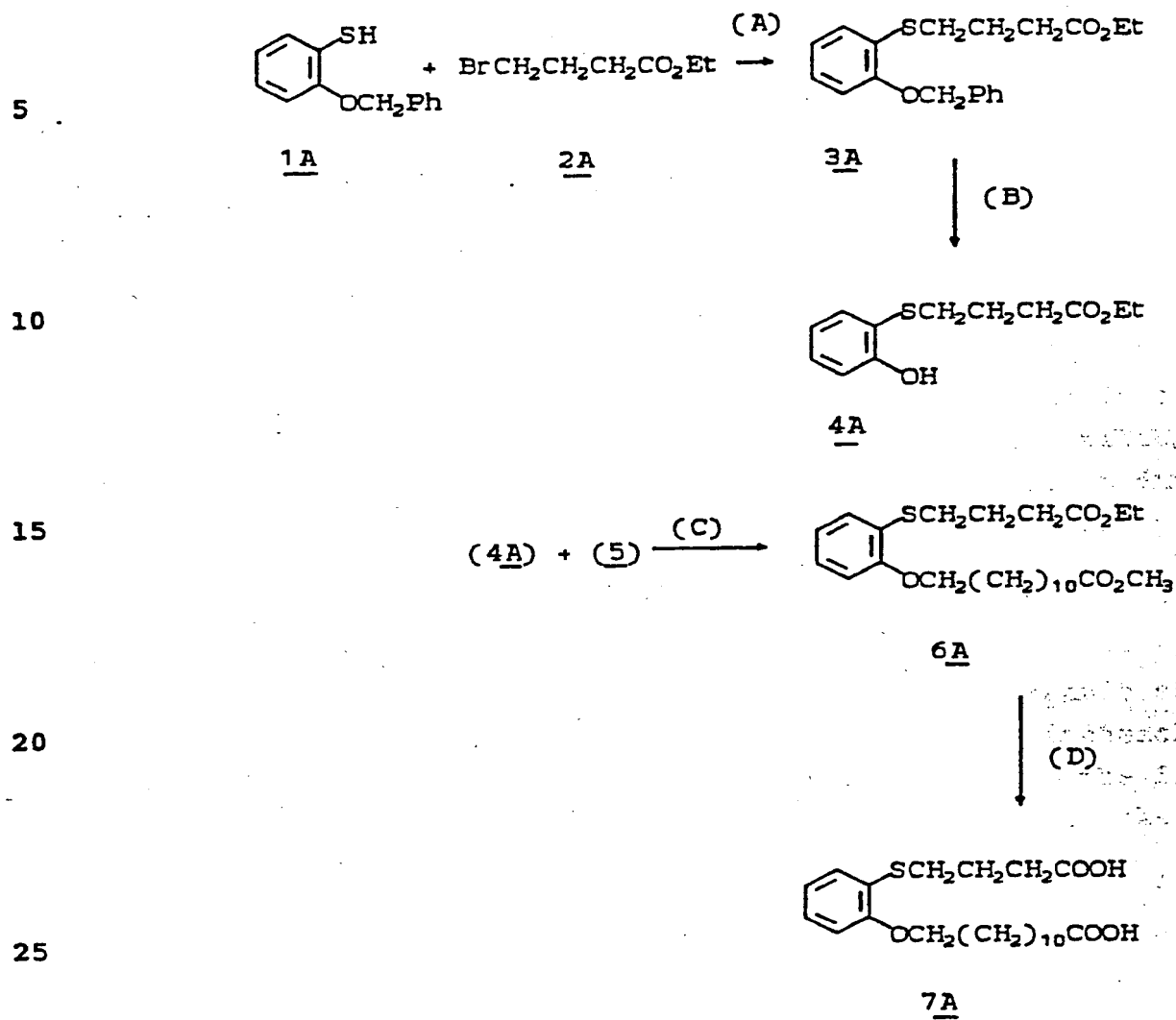


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FLOW CHART C-1



. - 102 -

Flow Sheet B-1 illustrates the specific synthesis of 7.

As seen, 2-benzyloxyphenol 1, ethyl 4-bromobutyrate 2 and anhydrous  $K_2CO_3$  in e.g., dry acetone are heated at reflux or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to give product ethyl 4-(2-benzyloxyphenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate is catalytically hydrogenated at room temperature under e.g. 40 psig of  $H_2$  in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-hydroxyphenoxy) butyrate 4 in Step (B).

Step (C) comprises reacting 4 and methyl 12-bromododecanoate 5 with potassium carbonate in acetone as in Step (A) to obtain the monomethyl ester 6.

In Step (D), the diester 6 is de-esterified by e.g., 2.5 N NaOH in MeOH/ $H_2O$  to yield the final product, diacid 7, upon acidification.

Flow Sheet C-1 illustrates the synthesis of the sulfur analog of 7 as 7A. This analogous procedure uses substantially the same steps as involved in Flow Sheet B.

It is also obvious from the above Flow Sheets that suitable replacement compounds for II and 2 with other substituted and unsubstituted halo alkyl esters, known in the art and described herein, and that suitable replacement of V and 5 with other bromoesters, available in the art and also described above will yield all of the compounds within the scope of the instant claims.

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Representative examples of compounds produced by this process include:

- 4-(2-(20-Carboxyeicosyloxy)phenoxy)butyric acid;  
4-(2-(19-Carboxynonadecyloxy)phenoxy)butyric acid;  
5 4-(2-(18-Carboxyoctadecyloxy)phenoxy)butyric acid;  
4-(2-(17-Carboxyheptadecyloxy)phenoxy)butyric acid;  
4-(2-(16-Carboxyhexadecyloxy)phenoxy)butyric acid;  
4-(2-(15-Carboxypentadecyloxy)phenoxy)butyric acid;  
4-(2-(14-Carboxytetradecyloxy)phenoxy)butyric acid;  
10 4-(2-(13-Carboxytridecyloxy)phenoxy)butyric acid;  
4-(2-(12-Carboxydodecyloxy)phenoxy)butyric acid;  
4-(2-(11-Carboxyundecyloxy)phenoxy)butyric acid;  
4-(2-(10-Carboxydecyloxy)phenoxy)butyric acid;  
4-(2-(9-Carboxynonyloxy)phenoxy)butyric acid;  
15 4-(2-(8-Carboxyoctyloxy)phenoxy)butyric acid;  
4-(2-(7-Carboxyheptyloxy)phenoxy)butyric acid;  
4-(2-(6-Carboxyhexyloxy)phenoxy)butyric acid;  
4-(2-(20-Carboxyeicosyloxy)phenylthio)butyric acid;  
4-(2-(19-Carboxynonadecyloxy)phenylthio)butyric acid;  
20 4-(2-(18-Carboxyoctadecyloxy)phenylthio)butyric acid;  
4-(2-(17-Carboxyheptadecyloxy)phenylthio)butyric acid;  
4-(2-(16-Carboxyhexadecyloxy)phenylthio)butyric acid;  
4-(2-(15-Carboxypentadecyloxy)phenylthio)butyric acid;  
4-(2-(14-Carboxytetradecyloxy)phenylthio)butyric acid;  
25 4-(2-(13-Carboxytridecyloxy)phenylthio)butyric acid;

30

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- 4-(2-(12-Carboxydodecyloxy)phenylthio)butyric acid;  
4-(2-(11-Carboxyundecyloxy)phenylthio)butyric acid;  
4-(2-(10-Carboxydecyloxy)phenylthio)butyric acid;  
4-(2-(9-Carboxynonyloxy)phenylthio)butyric acid;  
5 4-(2-(8-Carboxyoctyloxy)phenylthio)butyric acid;  
4-(2-(7-Carboxyheptyloxy)phenylthio)butyric acid;  
4-(2-(6-Carboxyhexyloxy)phenylthio)butyric acid;  
4-(2-(20-Carboxyeicosylthio)phenoxy)butyric acid;  
4-(2-(19-Carboxynonadecylthio)phenoxy)butyric acid;  
10 4-(2-(18-Carboxyoctadecylthio)phenoxy)butyric acid;  
4-(2-(17-Carboxyheptadecylthio)phenoxy)butyric acid;  
4-(2-(16-Carboxyhexadecylthio)phenoxy)butyric acid;  
4-(2-(15-Carboxypentadecylthio)phenoxy)butyric acid;  
4-(2-(14-Carboxytetradecylthio)phenoxy)butyric acid;  
15 4-(2-(13-Carboxytridecylthio)phenoxy)butyric acid;  
4-(2-(12-Carboxydodecylthio)phenoxy)butyric acid;  
4-(2-(11-Carboxyundecylthio)phenoxy)butyric acid;  
4-(2-(10-Carboxydecylthio)phenoxy)butyric acid;  
4-(2-(9-Carboxynonylthio)phenoxy)butyric acid;  
20 4-(2-(8-Carboxyoctylthio)phenoxy)butyric acid;  
4-(2-(7-Carboxyheptylthio)phenoxy)butyric acid;  
4-(2-(6-Carboxyhexylthio)phenoxy)butyric acid;  
4-(2-(20-Carboxyeicosylthio)phenylthio)butyric acid;  
4-(2-(19-Carboxynonadecylthio)phenylthio)butyric acid;  
25 4-(2-(18-Carboxyoctadecylthio)phenylthio)butyric acid;  
4-(2-(17-Carboxyheptadecylthio)phenylthio)butyric  
acid;  
4-(2-(16-Carboxyhexadecylthio)phenylthio)butyric  
acid;  
30 4-(2-(15-Carboxypentadecylthio)phenylthio)butyric  
acid;

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- 4-(2-(14-Carboxytetradecylthio)phenylthio)butyric acid;  
4-(2-(13-Carboxytridecylthio)phenylthio)butyric acid;  
5 4-(2-(12-Carboxydodecylthio)phenylthio)butyric acid;  
4-(2-(11-Carboxyundecylthio)phenylthio)butyric acid;  
4-(2-(10-Carboxydecylthio)phenylthio)butyric acid;  
10 4-(2-(9-Carboxynonylthio)phenylthio)butyric acid;  
4-(2-(8-Carboxyoctylthio)phenylthio)butyric acid;  
4-(2-(7-Carboxyheptylthio)phenylthio)butyric acid;  
4-(2-(6-Carboxyhexylthio)phenylthio)butyric acid;  
3-(2-(16-Carboxyhexadecyloxy)phenoxy)propionic acid;  
15 3-(2-(15-Carboxyisohexadecyloxy)phenoxy)butyric acid;  
3-(2-(14-Carboxytetradecyloxy)phenoxy)butyric acid;  
5-(2-(13-Carboxytridecyloxy)phenoxy)valeric acid;  
5-(2-(12-Carboxydodecyloxy)phenoxy)valeric acid;  
5-(2-(11-Carboxyisododecyloxy)phenoxy)valeric acid;  
20 4-(2-(11-Carboxyundecyloxy)phenoxy)valeric acid;  
4-(2-(10-Carboxydecyloxy)phenoxy)valeric acid;  
4-(2-(9-Carboxynonyloxy)phenoxy)valeric acid;  
6-(2-(9-Carboxynonyloxy)phenoxy)caproic acid;  
6-(2-(8-Carboxyoctyloxy)phenoxy)caproic acid;  
25 6-(2-(7-Carboxyisooctyloxy)phenoxy)caproic acid;  
7-(2-(7-Carboxyheptyloxy)phenoxy)enanthic acid;  
7-(2-(6-Carboxyhexyloxy)phenoxy)enanthic acid;  
7-(2-(5-Carboxyisohexyloxy)phenoxy)enanthic acid;  
2-(2-(12-Carboxydodecylthio)phenoxy)acetic acid;  
30 2-(2-(11-Carboxydecylthio)phenoxy)acetic acid;  
2-(2-(10-Carboxydecylthio)phenoxy)acetic acid;

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- 3-(2-(9-Carboxynonyloxy)phenylthio)propionic acid;  
3-(2-(12-Carboxydodecyloxy)phenylthio)propionic  
acid;  
5 3-(2-(11-Carboxyundecyloxy)phenylthio)propionic  
acid;  
3-(2-(11-Carboxyundecyloxy)phenylthio)butyric acid;  
3-(2-(11-Carboxyundecylthio)-4-methyl-phenylthio)  
butyric acid;  
10 3-(2-(12-Carboxydodecylthio)phenylthio)butyric  
acid;  
5-(2-(11-Carboxyundecylthio)phenylthio)valeric  
acid;  
5-(2-(10-Carboxydecyloxy)phenylthio)valeric acid;  
5-(2-(9-Carboxynonyloxy)phenylthio)valeric acid;  
15 3-(2-(12-Carboxydodecyloxy)phenylthio)valeric  
acid;  
3-(2-(11-Carboxydecyloxy)phenylthio)valeric acid;  
3-(2-(10-Carboxydecyloxy)phenylthio)valeric  
acid;  
20 6-(2-(9-Carboxynonylthio)phenylthio)caproic acid;  
6-(2-(12-Carboxydodecyloxy)phenylthio)caproic  
acid;  
6-(2-(11-Carboxyundecyloxy)phenylthio)caproic  
acid;  
25 6-(2-(11-Carboxyundecyloxy)-3-methylphenylthio)-  
enanthic acid;  
7-(2-(11-Carboxyundecyloxy)-4-methylphenylthio)-  
enanthic acid;  
7-(2-(12-Carboxydodecylthio)phenoxy)enanthic acid;  
30 4-(2-(11-Carboxyundecyloxy)4-methyl-phenoxy)butyric  
acid;



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- 4-(2-(10-Carboxydecyloxy)3-methylphenoxy)butyric acid;  
4-(2-(9-Carboxynonyloxy)5-methylphenoxy)butyric acid;  
4-(2-(12-Carboxydodecyloxy)6-methylphenoxy)butyric  
acid;  
5 4-(2-(12-Carboxydodecyloxy)6-methylphenoxy)butyric  
acid;  
4-(2-(11-Carboxyundecylthio)-3-(methylthio)phenoxy)-  
valeric acid;  
4-(2-(11-Carboxyundecylthio)-3-(methylsulfonyl)  
10 phenoxy)butyric acid;  
4-(2-(11-Carboxyundecyloxy)-4-(methylsulfonyl)  
phenoxy)butyric acid;  
4-(2-(12-Carboxydodecyloxy)5-ethyl-phenoxy)butyric  
acid;  
15 4-(2-(11-Carboxyundecyloxy)4-phenylphenoxy)butyric  
acid;  
4-(2-(10-Carboxydecyloxy)-3,5-dimethylphenoxy)butyric  
acid;  
4-(2-(9-Carboxynonyloxy)-4-fluoro-phenoxy)butyric  
20 acid;  
4-(2-(12-Carboxydodecyloxy)-5-(trifluoromethyl)-  
phenoxy)butyric acid;  
4-(2-(12-Carboxydodecylthio)-5-nitrophenoxy)butyric  
acid;  
25 4-(2-(11-Carboxyundecylthio)-4-methylphenoxy)valeric  
acid;  
4-(2-(11-Carboxyundecylthio)-3,5-di-methylphenoxy)-  
butyric acid;  
4-(2-(12-Carboxydodecyloxy)-4-(dimethylamino)phenoxy)-  
30 butyric acid;

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4-(2-(11-Carboxyundecyloxy)-5-(ethylamino)phenoxy)-  
butyric acid;

2-(2-(9-Carboxynonyloxy)phenoxy)propionic acid;

5 3-(2-(12-Carboxydodecyloxy)phenoxy)-3-methylpropionic  
acid;

4-(2-(10-Carboxydecyloxy)phenylthio)-3-methoxy-  
butyric acid;

4-(2-(9-Carboxynonyloxy)phenylthio)-3-ethoxy-  
butyric acid;

10 4-(2-(11-Carboxyundecyloxy)phenoxy)but-2-enoic acid;

4-(2-(9-Carboxynonyloxy)phenoxy)-2-butenic acid;

4-(2-(11-Carboxy-2-methylundecyloxy)phenoxy)butyric  
acid;

15 4-(2-(11-Carboxyundecyl-7-ene-oxy)phenoxy)butyric  
acid;

4-(2-(13-Carboxy-2-methylene-tri-decyloxy)phenoxy)-  
butyric acid;

4-(2-(11-Carboxyundecyloxy)phenylsulfonyl)butyric acid

4-(2-(11-Carboxyundecyloxy)phenylsulfinyl)butyric acid

20 4-(2-(11-Carboxyundecylsulfinyl)phenoxy)butyric acid

4-(2-(11-Carboxyundecylsulfonyl)phenoxy)butyric acid

4-(2-(11-Carboxyundecylsulfinyl)phenylsulfinyl)butyric  
acid

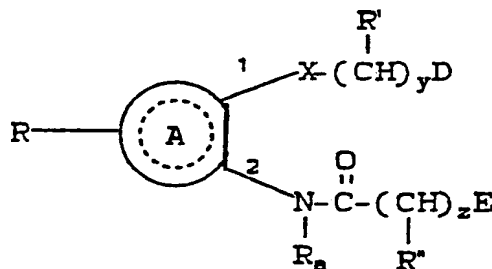
25 4-(2-(11-Carboxyundecylsulfonyl)phenylsulfonyl)butyric  
acid

and the like.

30

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Also included as a  $5\alpha$ -reductase inhibitor in this invention is an agent for the treatment of patterned baldness in combination with minoxidil is of the following formula:



wherein

A is an 1,2-disubstituted aromatic ring selected from

- 15
- (a) benzene, 1,2-disubstituted naphthalene;
  - (b) 5-6 membered heteroaromatic ring, containing 1-2 N atoms, 1 S or O atom, or combination thereof;

20 D and E are independently  $-\text{COOH}$ ,  $-\text{CONH}_2$ ,  $\text{CONHR}_b$ ,  $\text{COOR}_b$ ,  $\text{SO}_2\text{OH}$ ,  $\text{SO}_3(\text{OH})$ ,  $\text{SO}_2\text{NH}_2$ ,  $-\text{SSO}_2\text{ONa}$ ,  $\text{PH}(\text{O})(\text{OH})$ ,  $\text{P}(\text{O})(\text{OH})_2$ ;

X is O, S, SO or  $\text{SO}_2$ ;

R is H,

25  $\text{C}_1$ - $\text{C}_4$  alkyl,  
phenyl or substituted phenyl,  
halo,  
haloalkyl,  
hydroxy,  
30 carboxy,  
cyano,

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C<sub>1</sub>-C<sub>4</sub> alkoxy,  
C<sub>1</sub>-C<sub>4</sub> alkylthio,  
C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,  
C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl,  
5 nitro,  
amino,  
C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;

R' and R'' are independently

H,

10 halo,

C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,  
amino, or oxo, where CH-R' or CH-R''  
in the formula become -C=O;

R<sub>a</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl;

15 R<sub>b</sub> is C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

y is 1-6;

z is 6-20; and

20 wherein

R'  
|  
(CH)<sub>y</sub> and

R''  
|

(CH)<sub>z</sub> can independently represent substituted  
25 or unsubstituted alkyl radicals or alkenyl  
radicals containing at least one alkene bond;  
and pharmaceutically acceptable salts and esters  
thereof.

The compounds of the instant invention are  
30 inhibitors of the human testosterone-5 $\alpha$ -reductase .

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The scope of the compounds of the instant invention are described by the above-described formula.

5 In the description of the formula the following terms are used which are hereby defined:

X is preferably O or S, and particularly preferred is O.

10 "C<sub>1</sub>-C<sub>4</sub> alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl and "C<sub>1</sub>-C<sub>12</sub> alkyl" includes, alkyl up to 12 carbons including n-octyl, t-decyl, n-dodecyl.

"Phenyl C<sub>1</sub>-C<sub>4</sub> alkyl" includes benzyl, 2-phenethyl and the like.

15 "C<sub>1</sub>-C<sub>4</sub> alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy.

"Halo" includes fluoro, chloro, bromo or iodo.

20 By the term "heteroaromatic ring" as used herein is meant a 5-6 membered ring, containing 1-2 N-atoms, 1 S or O atom, or combination thereof, and includes: pyridine, thiophene, furan, imidazole, 1,3-thiazole, 1,3-oxazole, 1,2,3-thiadiazole, and  
25 the like. The limitation here being that the 1,2-disubstitution occurs on only ring carbons of the heteroaromatic ring. Preferred heteroaromatic rings are pyridine, furan and thiophene.

30 "Substituted phenyl" includes phenyl substituted by one or more of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halo, and the like, as defined above;

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representative examples include o, m-, p-methoxy phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

5 "Haloalkyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with one or more "halo" as defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.

10 "C<sub>1</sub>-C<sub>4</sub> alkylthio" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.

15 "C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

20 "C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one sulfonyl group, -SO<sub>2</sub>-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like.

25 "C<sub>1</sub>-C<sub>4</sub> mono or dialkyl amino" includes amino, substituted with one or more C<sub>1</sub>-C<sub>4</sub> alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, dimethylamino, diethylamino, methyl-t-butylamino, and the like.

30 The R group or groups on the benzene or heteroaromatic ring can be present initially in the process, e.g. phenyl, methyl, methoxy, cyano carbomethoxy, trifluoromethyl, ( as in the starting o-nitrophenol 1 in Flow Chart A) or added later

- 113 -

by a conventional reaction, e.g. chloro, as by chlorination, nitro by nitration, or created from a starting or added functional group present, e.g. converting a later added nitro group to an amino group by catalytic reduction, then alkylating to a mono or dialkylamine. An amino group can be subjected to diazotization to a hydroxy group, which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J. Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be alkylated to alkylthio, which can be oxidized to the corresponding sulfoxide or sulfone. Preferred substituents are H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant, salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, aceturate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

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$\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$ , where y is 1-6, preferably 3, can contain at least one R' substituent as defined above, and can be alkyl, e.g.,  $-\text{CH}_2$ ;  $-\text{CH}_2-\text{CH}_2$ ;  $-\text{CH}_2-\text{CH}_2-\text{CH}_2$ ,  
 5  $-\text{CH}$ ;  $-\text{CH}-\text{CH}_2$ ;  $-\text{CH}_2-\text{CH}$ ;  $-\text{CH}_2-\text{CH}-\text{CH}_2$ ;  
 $\begin{array}{c} \text{CH}_3 \quad \text{CH}_3 \quad \text{Cl} \quad \text{OCH}_3 \\ | \quad | \quad | \quad | \end{array}$   
 $-\text{CH}_2-\text{CH}-\text{CH}_2$ ;  
 $\begin{array}{c} \text{OCH}_2\text{CH}_3 \\ | \end{array}$   
 and the like.

10 An alkene bond can also be present in  
 $\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$ , e.g.,  $-\text{CH}_2-\text{CH}=\text{CH}$ ;  $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2$ ;  
 $-\text{CH}_2-\text{CH}_2-\text{CH}=\text{CH}$ ;  $-(\text{CH}_2)_3-\text{CH}=\text{CH}$ , and the like.

15  $\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$ , where z is 6-20, preferably 8-14, can contain at least one R'' substituent as defined above, and can be alkyl; e.g.,  $-(\text{CH}_2)_6$ -  
 $-(\text{CH}_2)_{20}$ ;  $-(\text{CH}_2)_9-\text{CH}$ ;  
 $\begin{array}{c} \text{CH}_3 \\ | \end{array}$   
 20  $-\text{CH}_2-\text{CH}-(\text{CH}_2)_9-$ ;  $-(\text{CH}_2)_5-\text{CH}-(\text{CH}_2)_4-$ ;  
 $\begin{array}{c} \text{F} \quad \text{OCH}_3 \\ | \quad | \end{array}$   
 and the like.

25 An alkene bond can also be present in  
 $\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$ , e.g.,  $-\text{CH}_2-\text{CH}=\text{CH}-(\text{CH}_2)_8-$ ;  
 $-(\text{CH}_2)_8-\text{CH}=\text{CH}-(\text{CH}_2)_2-$ ;  $-(\text{CH}_2)_9-\text{CH}=\text{CH}-(\text{CH}_2)_9-$ ;  
 $(\text{CH}_2)_4-\text{CH}=\text{CH}-(\text{CH}_2)_4-$ ; and the like.

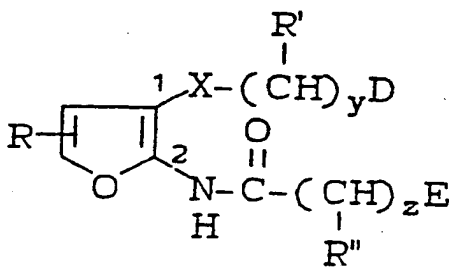
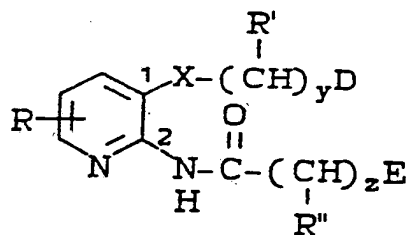
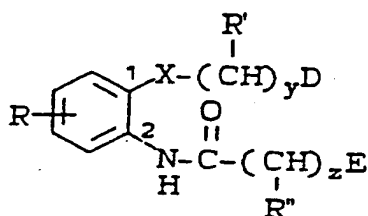
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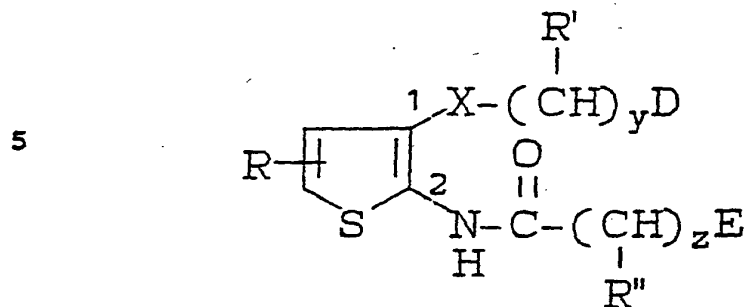
- 115 -

Preferred is where one R' or R'' is H and particularly preferred is where both  $\overset{\text{R}'}{\underset{|}{\text{CH}}}_y$  and  $\overset{\text{R}''}{\underset{|}{\text{CH}}}_z$  are alkyl.

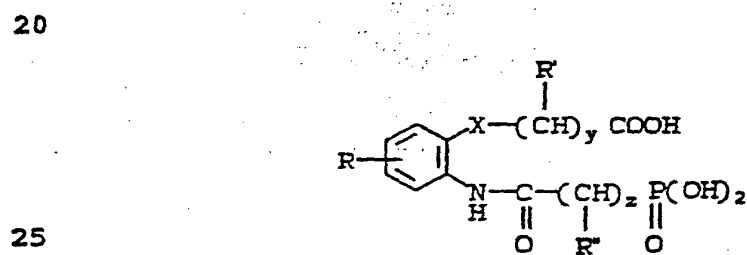
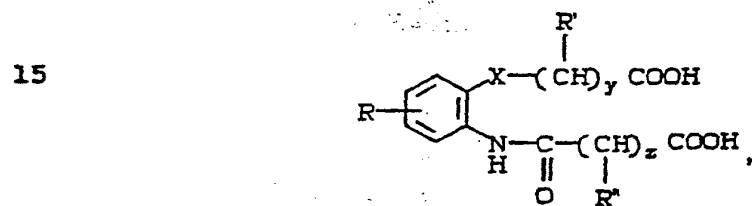
Representative compounds of the instant invention within the above general formula are given by the following, structures;



- 116 -



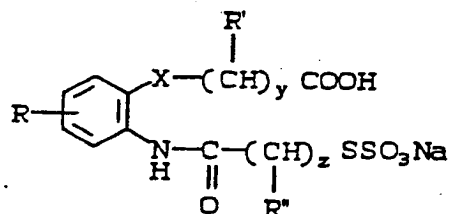
10 Particularly preferred are the following compounds:



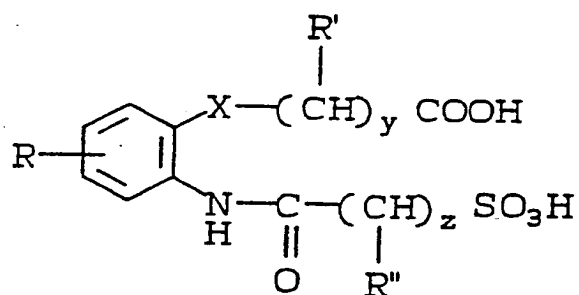
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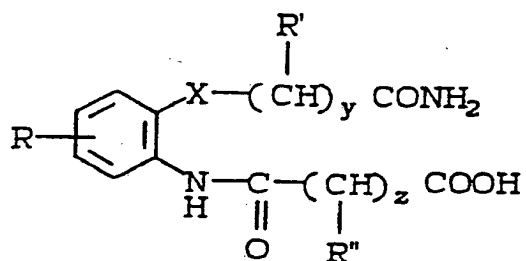


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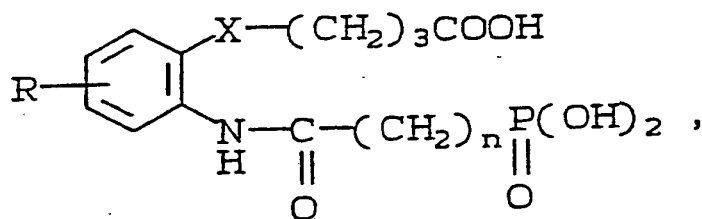
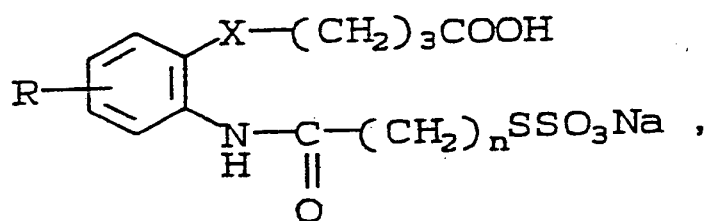
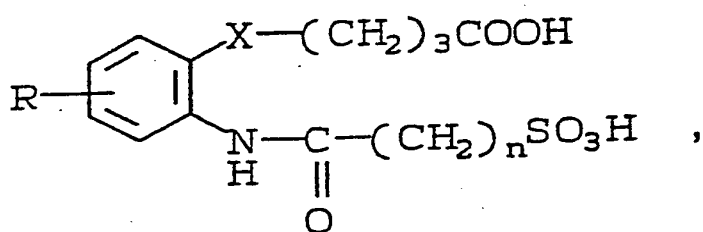
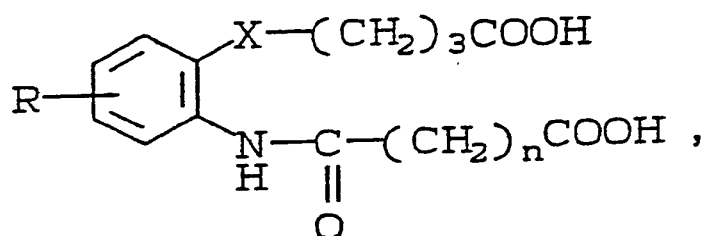
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where X is O or S and R, R', R'', y and z are as defined above.

30

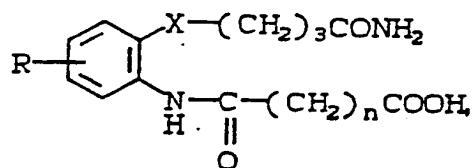
- 118 -

Preferred compounds within this class are:



- 119 -

5

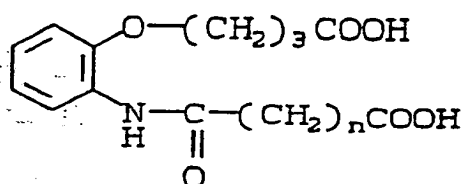


where X is O or S, and n is 8-14.

10

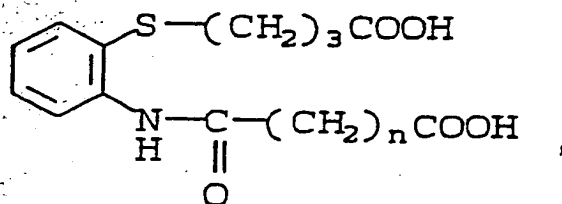
Also preferred compounds are within these classes are:

15



where n is 8-14.

20



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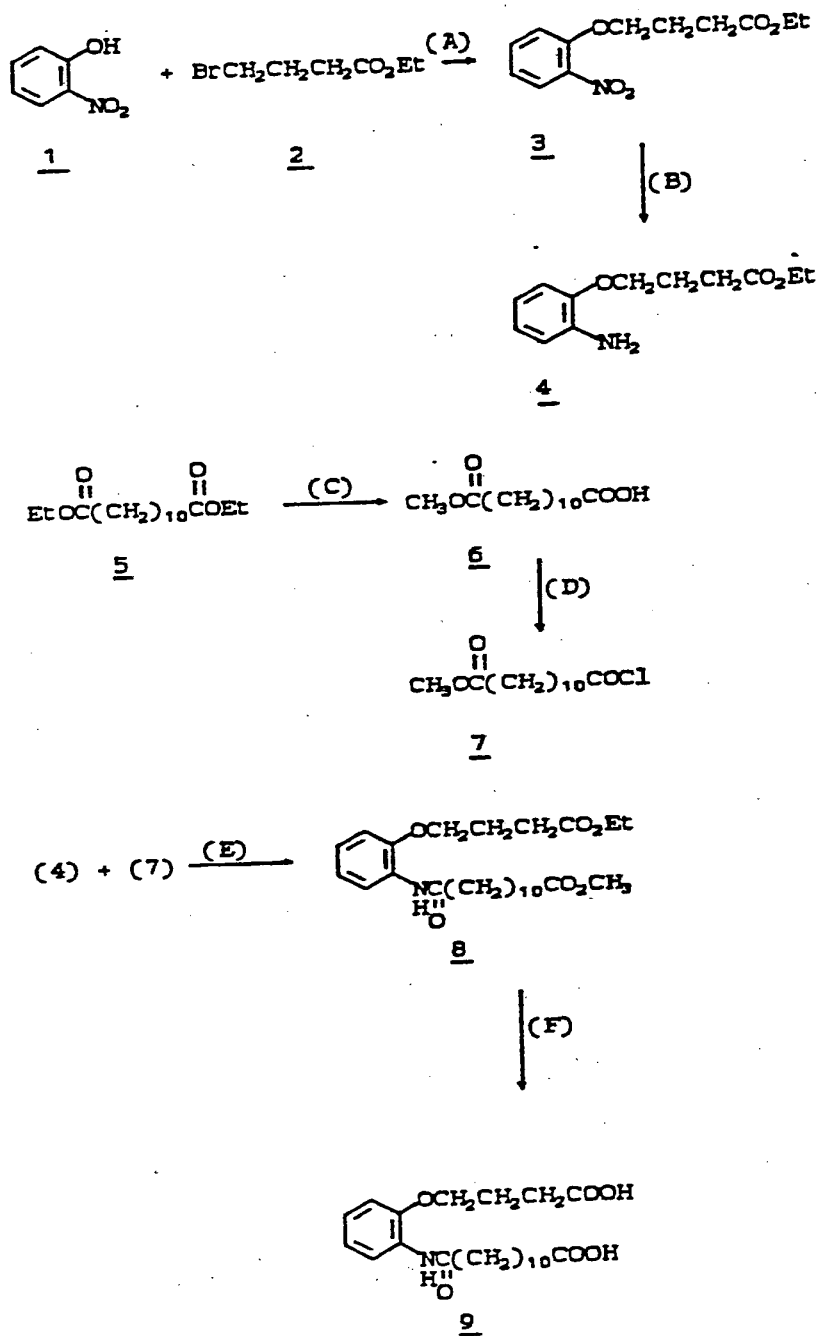
where n is 8-14.

30

The compounds of the instant invention can be made by the procedures outlined in the following Flowcharts.

- 120 -

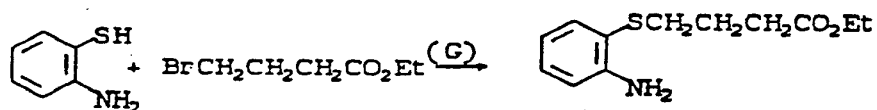
## FLOW CHART A-2



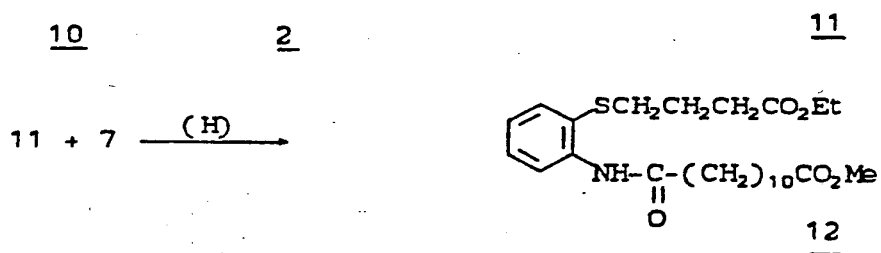
- 121 -

FLOW CHART B-2

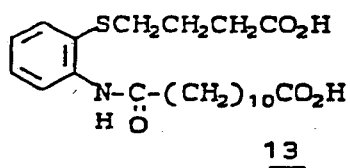
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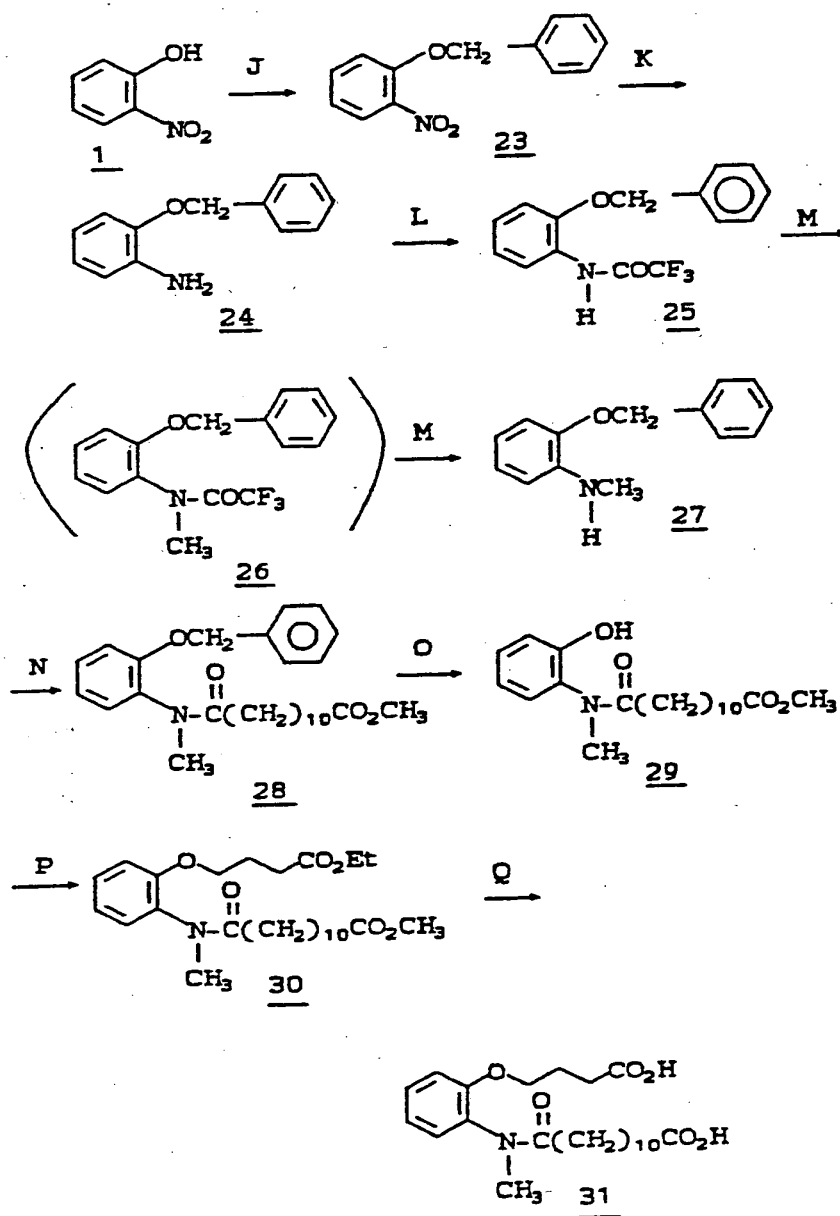
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## FLOW CHART C-2





- 123 -

## FLOW CHART D-2

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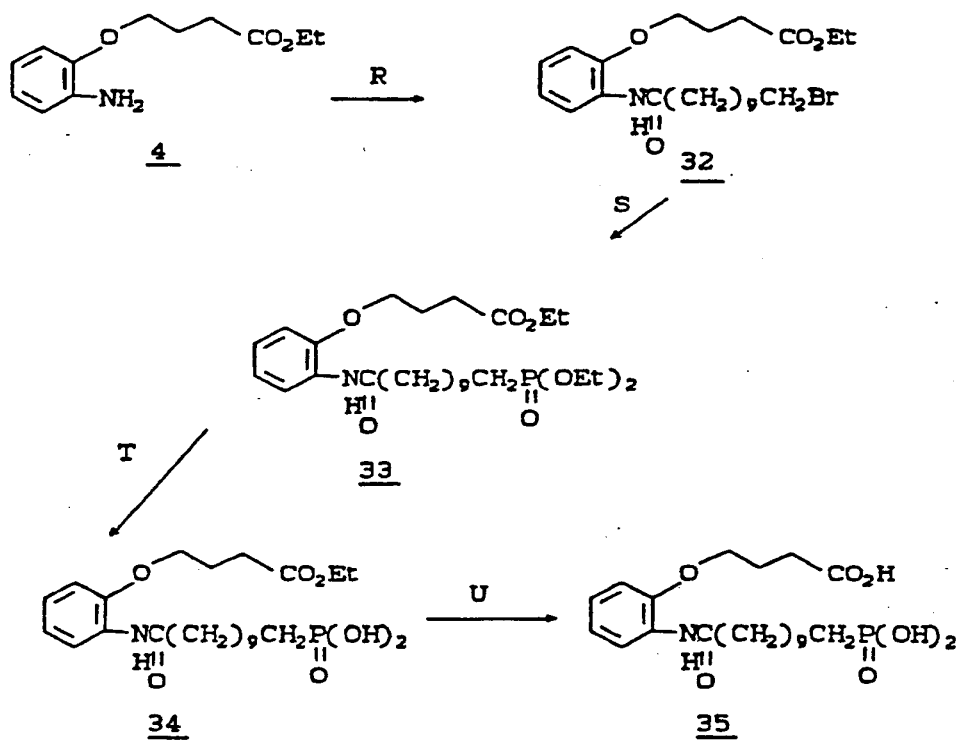
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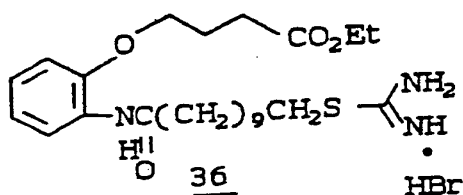
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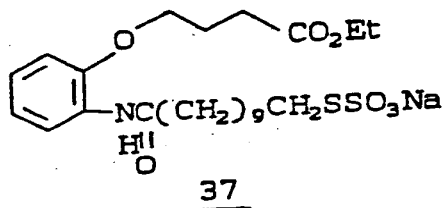
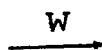
FLOW CHART E-2

5

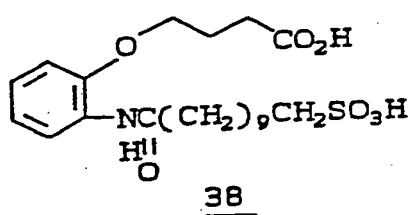
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HBr

10

32

15



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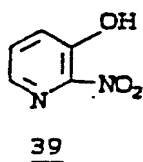
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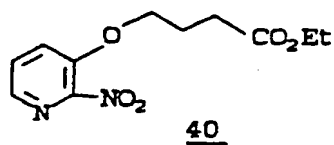
- 125 -

## FLOW CHART F-2

5

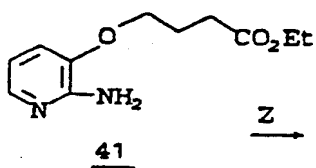


X

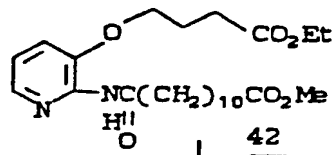


Y

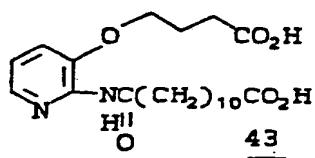
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Z



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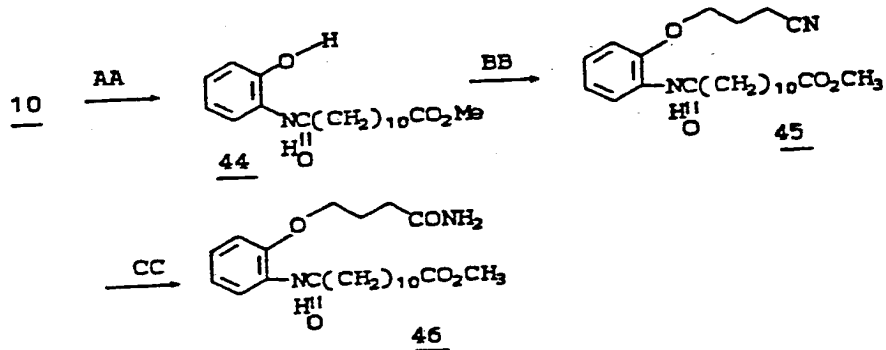
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## FLOW CHART G-2



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FLOW CHART H-2

44 BrCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO<sub>2</sub>Et > (9) (alternate route to 9)

5 As seen in Flow Chart A-2, o-nitrophenol 1, ethyl 4-bromobutyrate 2 and anhydrous K<sub>2</sub>CO<sub>3</sub> in e.g., dry acetone are heated at reflux or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to product ethyl  
10 4-(2-nitrophenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate is catalytically hydrogenated at room temperature under e.g. 40 psig of H<sub>2</sub> in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-aminophenoxy)butyrate  
15 4 in Step (B).

Step (C) comprises reacting diethyl dodecanoate 5 with barium hydroxide octahydrate in methanol at ambient temperature to obtain the monomethyl ester 6.

20 In Step (D) the mono ester mono acid 6 is refluxed with thionyl chloride for about 5 hours to produce the mono acid chloride, mono methyl ester 7.

Step (E) comprises the reaction of the mono acid chloride 7 with the amine 4 at e.g., 0-10°C in  
25 e.g., dry ether in the presence of a hydrogen acceptor e.g., triethylamine, to produce the amide 8.

In Step (F), the ether-amide diester 8 is de-esterified by e.g., 2.5 N NaOH in MeOH/H<sub>2</sub>O to yield after acidification the final product, diacid 9.

30 Flow Chart B-2 illustrates the synthesis of the corresponding thio compounds.

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Step (G) illustrates the reaction of o-aminobenzenethiol with ethyl 4-bromobutyrate which can be carried out in e.g., dry dimethoxyethane, under dry N<sub>2</sub>, in the presence of a proton acceptor, e.g., dry powdered K<sub>2</sub>CO<sub>3</sub>, to produce 11.

Step (H) illustrates the acylation of the amino group of 11 with ethyl 11-bromoundecanoate in a dry solvent, e.g., dry ether, at 0°C in the presence of an acid acceptor, e.g., pyridine.

Step (I) illustrates the hydrolysis of the diester to the final diacid 13, which can be accomplished with, e.g., NaOH/MeOH.

As seen in Flow Chart C-2, o-nitrophenol is benzylated under the same conditions as in Step (A).

Step (K) shows the reduction of the nitro group using e.g., Raney Ni in ethanol/NH<sub>3</sub> under 40 psig H<sub>2</sub>.

Step (L) shows the trifluoroacetylation of 24 using e.g., trifluoroacetic anhydride in dry ether and powdered dry sodium carbonate.

Step (M) shows the N-methylation which can be accomplished using, e.g., methyl iodide in dry acetone and dry powdered KOH followed by removal of the N-trifluoroacetyl group with MeOH/H<sub>2</sub>O.

Step (N) shows the N-acylation of 27, using an acid chloride, e.g., 7, in e.g., dry methylene chloride and pyridine at 0°C.

Step (O) shows the debenzylation of 28, which can be accomplished by e.g., 10% Pd/C in MeOH under a H<sub>2</sub> atmosphere.

Step (P) shows the O-alkylation of 29 using e.g., ethyl 4-bromobutyrate and K<sub>2</sub>CO<sub>3</sub> in anhydrous acetone.

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Step (Q) shows hydrolysis of the diester 30 to the diacid 31 by hydrolysis as e.g., described for Step (F).

5 Flow Chart D-2 shows the production of phosphonate type esters and acids.

Step (R) shows the condensation of 4 with 11-bromoundecanoic acid in anhydrous methylene chloride using N,N'-dicyclohexylcarbodiimide and 4-dimethylaminopyridine to produce the important  
10 bromo intermediate 32.

Step (S) shows the reaction of 32 with triethylphosphite at e.g., 180°C under N<sub>2</sub> to produce the phosphonate ester 33.

Step (T) converts 33 via bromotrimethyl-  
15 silane to the monoacid 34.

Step (U) uses the similar hydrolysis conditions of Step (F) to produce the phosphonic-carboxylic diacid 35.

The corresponding phosphinic acids can be  
20 analogously made from 32 by known procedures in the art.

Flow Chart E-2 illustrates the synthesis of the sulfonic acid types of the invention compounds.

Step (V) shows reaction of the intermediate  
25 32 with thiourea in EtOH/H<sub>2</sub>O under N<sub>2</sub> at 90°C to yield the isothiuronium salt 36.

Step (W) shows the reaction of 32 with sodium thiosulfate under the conditions of Step (V) to yield the thiosulfate ester 37.

30 Further oxidation of esters 36 or 37 via the Showell or Ziegler procedures described in Step W in the examples yields the corresponding sulfonic acid 38.

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The corresponding sulfinic acid can be prepared from 36 by the procedure of J. M. Sprague and T. B. Johnson, JACS 59, 2440 (1937).

5 The corresponding sulfonamide can be produced from the sulfonic acid 38, by protecting, e.g., the carboxylic acid via an ester, converting the sulfonic acid to a sulfonyl chloride, treating the sulfonyl chloride with ammonia and then hydro-  
10 lyzing the protected carboxylic ester to the corresponding acid.

Flow Chart F-2 shows the corresponding synthesis of the pyridine analogs of 8 and 9.

In Step (X), the nitrohydroxy pyridine is O-alkylated first using conditions analogous  
15 to Step (A) to produce 40.

Step (Y) shows reducing the nitro group in the same manner as described for Step (B).

Step (Z) shows acylating the amino group in the same manner as described for 8 in Step (E)  
20 to produce the diester 42. Hydrolysis produces the diacid 43.

Flow Chart G-2 shows the production of some amides 46 of the invention.

25 In Step (AA), o-aminophenol is reacted directly with 7 under the conditions of Step (E) to produce the N-acylated phenol 44.

In Step (BB), O-alkylation of 44 as carried out using 4-bromobutyronitrile under conditions similar to Step (A), produces 45.

30 Step (CC) shows the hydrolysis of the nitrile to the amide 46 using  $MnO_2$  in methylene chloride.



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Flow Chart H-2 illustrates an alternate route to 9 by starting with o-aminophenol, acylating to produce 44, then reacting 44 under the conditions of Step (A) to produce 8, then hydrolysis using Step (F) to yield 9.

Thus, by using the above described methods in the Flow Charts and the reaction starting materials and reagents described herein, all of the compounds described and encompassed by the claim can be synthesized by one skilled in the art.

It is obvious that other nitrophenols can be substituted for 1 in Flow Charts A-2 and C-2 to provide the scope of the compounds covered by this invention and include the following:

- 2-nitrophenol
- 2-nitro-6-methylphenol
- 2-nitro-5-methylphenol
- 2-nitro-4-methylphenol
- 2-nitro-3-methylphenol
- 2-nitro-4-phenylphenol
- 2-nitro-5-phenylphenol
- 2-nitro-4-chlorophenol
- 2-nitro-4-fluorophenol
- 2-nitro-4-trifluoromethylphenol
- 2-nitro-4-hydroxyphenol
- 2-nitro-4-methoxyphenol
- 2-nitro-6-ethoxyphenol
- 2-nitro-4-methylthio-phenol
- 2-nitro-4-methylsulfinylphenol
- 2-nitro-4-methylsulfonylphenol

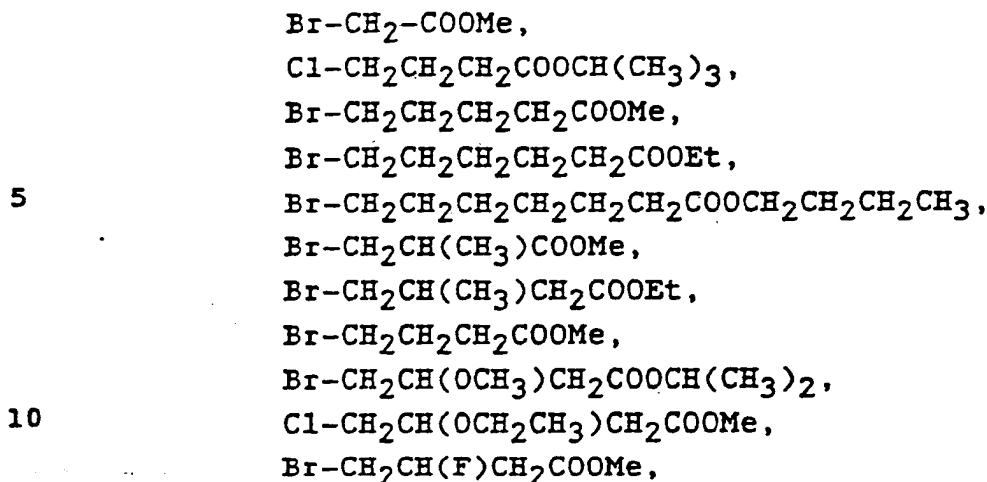
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- 4-nitro-3-hydroxypyridine  
3-nitro-4-hydroxy-5-methylpyridine  
3-nitro-4-hydroxy-6-methylpyridine  
2-methyl-3-nitro-4-hydroxypyridine  
5 2-hydroxy-3-nitro-5-phenylpyridine  
2-nitro-3-hydroxy-5-phenylpyridine  
2-hydroxy-3-nitro-5-chloropyridine  
2-nitro-3-hydroxy-5-trifluoromethylpyridine  
2-methoxy-4-nitro-5-hydroxypyridine  
10 3-nitro-4-hydroxy-5-ethoxypyridine  
2-methylthio-4-nitro-5-hydroxypyridine  
2-nitro-3-hydroxy-thiophene  
3-nitro-4-hydroxy-thiophene  
3-hydroxy-2-nitro-5-methyl-thiophene  
15 3-hydroxy-2-nitro-4-methyl-thiophene  
2-hydroxy-3-nitro-5-phenyl-thiophene  
2-nitro-3-hydroxy-4-phenyl-thiophene  
2-hydroxy-3-nitro-4-chlorothiophene  
2-hydroxy-3-nitro-4-fluorothiophene  
20 and the like.

It is obvious that suitable replacement compounds for 2 with other halo alkyl esters, known in the art, and that suitable replacement of 6 with  
25 other diesters, available in the art, will yield all of the ether-amide derivatives within the scope of the claims.

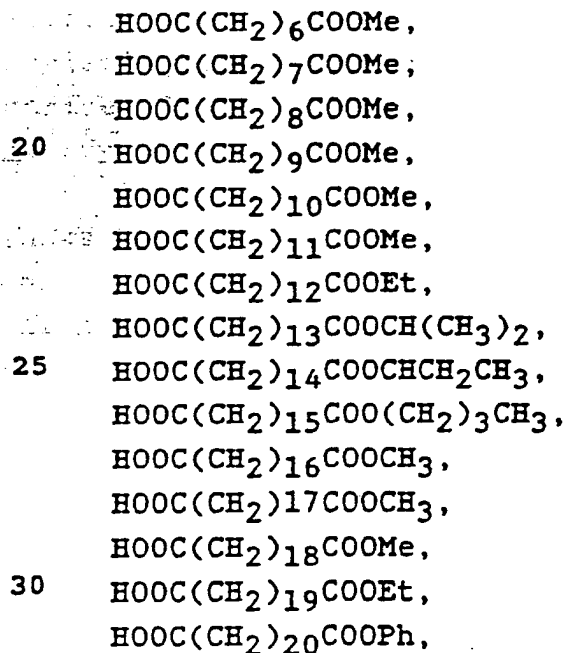
Representative examples of 2 useful in  
30 the invention process include, but are not limited to:

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and the like.

15 Representative examples of other compounds  
substitutable for 6 and useful in the invention are:



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$\text{HOOC}(\text{CH}_2)_{10}\text{COOCH}_2\text{Ph},$   
 $\text{HOOCCH}(\text{CH}_3)-(\text{CH}_2)_{10}\text{COOMe},$   
 $\text{HOOC}-\text{CH}_2\text{CH}-(\text{CH}_3)(\text{CH}_2)_{10}\text{COOMe},$   
 $\text{HOOC}-\text{CH}_2\text{CH}_3\text{CH}(\text{CH}_3)\text{CH}_2\text{COOEt},$   
 5  $\text{HOOC}-\text{CH}_2\text{CH}_2\underset{\text{Cl}}{\text{CH}}-\text{CH}_2\text{COOEt}$   
 $\text{HOOC}-\text{CH}_2\text{CH}(\text{OCH}_3)(\text{CH}_2)_7\text{COOCH}(\text{CH}_3)_2,$   
 where Ph is phenyl,  
 and the like.

10

Representative examples of compounds produced by this process include those in the following list.

The nomenclature used herein for the acid radicals is:

15

$\text{P}(\text{O})(\text{OH})_2$ , phosphono;  
 $-\text{COOH}$ , carboxy;  
 $-\text{CONH}_2$ , aminocarbonyl;  
 $-\text{SO}_3\text{H}$ , sulfo;  
 $-\text{SO}_2\text{H}$ , sulfinio;  
 20  $-\text{SSO}_3\text{H}$ , thiosulfato, as the sodium salt.

20

4-(2-(20-Carboxyeicosanoylamino)phenoxy)butyric acid;

4-(2-(19-Carboxynonadecanoylamino)phenoxy)butyric acid;

25

4-(2-(18-Carboxyoctadecanoylamino)phenoxy)butyric acid;

4-(2-(17-Carboxyheptadecanoylamino)phenoxy)butyric acid;

30

4-(2-(16-Carboxyhexadecanoyl-N-methylamino)phenoxy)-butyric acid;

4-(2-(15-Carboxypentadecanoylamino)phenoxy)butyramide;

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- 4-(2-(14-Carboxytetradecanoylamino)phenoxy)butyric acid;
- 4-(2-(13-Carboxyl-tridecanoylamino)phenoxy)butyric acid;
- 5 4-(2-(12-Carboxy-dodecanoylamino)phenoxy)butyric acid;
- 4-(2-(11-Carboxy-undecanoylamino)phenoxy)butyric acid;
- 10 4-(2-(10-Carboxy-decanoylamino)phenoxy)butyric acid;
- 4-(2-(9-Carboxy-nonanoylamino)phenoxy)butyric acid;
- 4-(2-(8-Carboxy-octanoylamino)phenoxy)butyric acid;
- 4-(2-(7-Carboxy-heptanoylamino)phenoxy)butyric acid;
- 4-(2-(6-Carboxy-hexanoylamino)butyric acid;
- 15 4-(2-(20-Carboxyeicosanoylamino)phenylthio)butyric acid;
- 4-(2-(19-Carboxynonadecanoylamino)phenylthio)butyric acid;
- 20 4-(2-(18-Carboxy-octadecanoylamino)phenylthio)butyric acid;
- 4-(2-(17-Carboxyheptadecanoyl-N-ethylamino)phenylthio)butyric acid;
- 4-(2-(16-Carboxyhexadecanoylamino)phenylthio)butyric acid;
- 25 4-(2-(15-Carboxypentadecanoylamino)phenylthio)butyric acid;
- 4-(2-(14-Carboxytetradecanoylamino)phenylthio)butyramide;
- 4-(2-(13-Carboxytridecanoylamino)phenylthio acid;
- 30 4-(2-(12-Carboxy-dodecanoylamino)phenylthio)butyric acid;

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- 4-(2-(11-Carboxy-undecanoylamino)phenylthio)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)phenylthio)butyric acid;
- 5 4-(2-(9-Carboxynonanoylamino)phenylthio)butyric acid;
- 4-(2-(8-Carboxyoctanoylamino)phenylthio)butyric acid;
- 4-(2-(7-Carboxyheptanoylamino)phenylthio)butyric acid;
- 4-(2-(6-Carboxyhexanoylamino)phenylthio)butyric acid;
- 10 3-(2-(16-Carboxyhexadecanoylamino)phenoxy)propionic acid;
- 4-(2-(15-Carboxyisohexadecanoylamino)phenoxy)butyric acid;
- 4-(2-(14-Carboxytetradecanoylamino)phenoxy)butyric acid;
- 15 5-(2-(13-Carboxytridecanoylamino)phenoxy)valeric acid;
- 5-(2-(12-Carboxydodecanoylamino)phenoxy)valeric acid;
- 5-(2-(11-Carboxyisododecanoylamino)valeric acid;
- 20 4-(2-(11-Carboxyundecanoylamino)isovaleric acid;
- 4-(2-(10-Carboxydecanoylamino)isovaleric acid;
- 5-(2-(9-Carboxynonanoylamino)phenoxy)valeric acid;
- 6-(2-(9-Carboxynonanoylamino)phenoxy)caproic acid;
- 6-(2-(8-Carboxyoctanoylamino)phenoxy)caproic acid;
- 25 6-(2-(7-Carboxyisooctanoylamino)phenoxy)caproic acid;
- 7-(2-(7-Carboxyheptanoylamino)phenoxy)enanthic acid;
- 7-(2-(6-Carboxyhexanoylamino)phenoxy)enanthic acid;
- 7-(2-(5-Carboxyisohexanoylamino)phenoxy)enanthic acid;
- 30 2-(2-(12-Carboxydodecanoylamino)phenoxy)acetic acid;

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- 2-(2-(11-Carboxyundecanoylamino)phenoxy)acetic acid;
- 2-(2-(10-Carboxydecanoylamino)phenoxy)acetic acid;
- 3-(2-(9-Carboxynonanoylamino)phenoxy)propionic acid;
- 5 3-(2-(12-Carboxydodecanoylamino)phenylthio)propionic acid;
- 3-(2-(11-Carboxyundecanoylamino)phenylthio)propionic acid;
- 3-(2-(11-Carboxyundecanoylamino)phenylthio)isobutyric acid;
- 10 5-(2-(11-Carboxyundecanoylamino)phenylthio)valeric acid;
- 5-(2-(10-Carboxydecanoylamino)phenylthio)valeric acid;
- 15 5-(2-(9-Carboxynonanoylamino)phenylthio)valeric acid;
- 4-(2-(12-Carboxydodecanoylamino)phenylthio)isovaleric acid;
- 4-(2-(11-Carboxydecanoylamino)phenylthio)isovaleric acid;
- 20 4-(2-(10-Carboxydecanoylamino)phenylthio)isovaleric acid;
- 6-(2-(9-Carboxynonanoylamino)phenoxy)caproic acid;
- 6-(2-(12-Carboxydodecanoylamino)phenylthio)caproic acid;
- 25 6-(2-(11-Carboxyundecanoylamino)phenylthio)caproic acid;
- 7-(2-(11-Carboxyundecanoylamino)-3-methylphenylthio)-  
  enanthic acid;
- 7-(2-(11-Carboxyundecanoylamino)-4-methylphenylthio)-  
  enanthic acid;
- 30 7-(2-(12-Carboxydodecanoylamino)phenoxy)enanthic acid;

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- 4-(2-(11-Carboxyundecanoylamino)4-methyl-phenoxy)  
butyric acid;
- 4-(2-(10-Carboxydecanoylamino)3-methylphenoxy)butyric  
acid;
- 5 4-(2-(9-Carboxynonanoylamino)5-methylphenoxy)butyric  
acid;
- 4-(2-(12-Carboxydodecanoylamino)6-methylphenoxy)  
butyric acid;
- 10 4-(2-(11-Carboxydecanoylamino)3-chloro)phenylthio)-  
butyric acid;
- 4-(2-(10-Carboxydecanoylamino)4-methylphenoxy)butyric  
acid;
- 4-(2-(9-Carboxynonanoylamino)5-fluoromethyl)phenyl-  
thio)butyric acid;
- 15 4-(2-(12-Carboxydodecanoylamino)6-methylphenoxy)-  
butyric acid;
- 5-(2-(11-Carboxyundecanoylamino)-3-methylthio)-  
phenoxy)valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-3-methylsulfonyl-  
phenoxy)butyric acid;
- 20 4-(2-(11-Carboxyundecanoylamino)-4-methylsulfonyl)-  
phenylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)5-ethyl-phenoxy)-  
butyric acid;
- 25 4-(2-(11-Carboxyundecanoylamino)4-phenylphenoxy)-  
butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-3,5-dimethylphenoxy)-  
butyric acid;
- 4-(2-(9-Carboxynonanoylamino)-4-fluoro-phenoxy)butyric  
30 acid;



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- 4-(2-(12-Carboxydodecanoylamino)-5-trifluoromethyl-  
phenoxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-5-hydroxy)phenylthio)  
butyric acid;
- 5 4-(2-(10-Carboxydecanoylamino)-4-hydroxy)phenylthio)-  
butyric acid;
- 4-(2-(9-Carboxynonanoylamino)-3,5-dimethoxy-  
phenylthio)butyric acid;
- 10 4-(2-(12-Carboxydodecanoylamino)-5-nitrophenoxy)-  
butyric acid;
- 5-(2-(11-Carboxyundecanoylamino)-4-nitrophenoxy)-  
valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-5-amino-3-methyl-  
phenoxy)butyric acid;
- 15 4-(2-(11-Carboxyundecanoylamino)-5-amino-4-methyl-  
phenylthio)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-4-dimethylamino-  
phenoxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-5-ethylamino-  
20 phenoxy)butyric acid;
- 3-(2-(12-Carboxydodecanoylamino)phenoxy)-3-  
methylpropionic acid;
- 3-(2-(11-Carboxydecanoylamino)phenylthio)-2-chloro-  
propionic acid;
- 25 4-(2-(10-Carboxydecanoylamino)phenylthio)-3-methoxy-  
butyric acid;
- 4-(2-(9-Carboxynonanoylamino)phenylthio)-3-ethoxy-  
butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-4-methyl-3-pyridyl-  
30 oxy)butyric acid;

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- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-pyridyl-  
oxy)butyric acid;
- 4-(2-(10-Carboxydecanoylamino)-5-methyl-3-pyridyloxy)-  
butyric acid;
- 5 4-(2-(9-Carboxynonanoylamino)5-hydroxy-3-pyridyloxy)-  
butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-6(dimethylamino)-3-  
pyridyloxy)butyric acid;
- 10 4-(2-(11-Carboxydecanoylamino)-3-pyridylthio)-butyric  
acid;
- 4-(2-(10-Carboxydecanoylamino)-6-methylsulfonyl-3-  
pyridyloxy)butyric acid;
- 4-(2-(9-Carboxynonanoylamino)5-chloro-3-pyridylthio)-  
butyric acid;
- 15 4-(2-(12-Carboxydodecanoylamino)-5-methylpyridylthio)-  
butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)5-methylsulfonyl-3-  
pyridylthio)butyric acid;
- 20 4-(2-(11-Carboxyundecanoylamino)-6-methyl-3-pyridyl-  
thio)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4,6-dimethyl-3-  
pyridyloxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-methylthio-3-  
pyridyloxy)butyric acid;
- 25 4-(2-(11-Carboxyundecanoylamino)pyridyloxy)butyric  
acid;
- 4-(2-(10-Carboxydecanoylamino)-5-methoxy-3-pyridyloxy)  
butyric acid;
- 30 4-(2-(9-Carboxynonanoylamino)-4-fluoro-6-methyl-3-  
pyridyloxy)butyric acid;

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- 4-(2-(12-Carboxydodecanoylamino)5-methylamino-3-pyridyloxy)butyric acid;  
4-(2-(11-Carboxyundecanoylamino)4-phenyl-3-pyridylthio)butyric acid;  
5 4-(2-(10-Carboxydecanoylamino)5-methyl-3-pyridylthio)-butyric acid;  
4-(2-(9-Carboxynonanoylamino)6-methoxy-3-pyridylthio)butyric acid;  
4-(2-(12-Carboxydodecanoylamino)-6-trifluoromethyl-3-pyridyloxy)butyric acid;  
10 5-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienyloxy)valeric acid;  
4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienyloxy)butyric acid;  
15 4-(2-(11-Carboxyundecanoylamino)-4-methyl)-3-thienylthio)butyric acid;  
4-(2-(12-Carboxydodecanoylamino)-5-methyl-3-thienylthio)butyric acid;  
4-(2-(11-Carboxyundecanoylamino)-4-methyl-3-thienylthio)butyric acid;  
20 4-(2-(10-Carboxydecanoylamino)-5-methyl-3-thienylthio)butyric acid;  
4-(2-(9-Carboxynonanoylamino)-4-hydroxy-3-thienyloxy)-butyric acid;  
25 4-(2-(12-Carboxydecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;  
4-(2-(11-Carboxydecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;  
4-(2-(10-Carboxydecanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;  
30

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- 4-(2-(9-Carboxynonanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-trifluoromethyl-3-thienyloxy)butyric acid;
- 5 5-(2-(11-Carboxyundecanoylamino)-5-chloro-3-thienyloxy)valeric acid;
- 4-(2-(11-Carboxyundecanoylamino)-4-methyl-5-phenyl-3-thienyloxy)butyric acid;
- 10 4-(2-(11-Carboxyundecanoylamino)-5-methylamino-3-thienyloxy)butyric acid;
- 4-(2-(12-Carboxydodecanoylamino)-5-dimethylamino-3-thienyloxy)butyric acid;
- 4-(2-(11-Carboxyundecanoylamino)-3-thienyloxy)butyric acid;
- 15 4-(2-(20-Phosphonoeicosanoylamino)phenoxy)butyric acid;
- 4-(2-(19-Phosphonononadecanoylamino)phenoxy)butyric acid;
- 4-(2-(17-Sulfoheptadecanoylamino)phenoxy)butyric acid;
- 20 4-(2-(16-Sulfinohexadecanoyl-N-methylamino)phenoxy)-butyric acid;
- 4-(2-(15-Thiosulfatopentadecanoylamino)phenoxy)butyramide sodium salt;
- 25 4-(2-(14-Phosphonetetradecanoyl-N-methylamino)phenoxy)butyric acid;
- 4-(2-(12-Sulfododecanoylamino)phenoxy)butyric acid;
- 4-(2-(11-Sulfoundecanoylamino)phenoxy)butyric acid;
- 4-(2-(10-Sulfinodecanoylamino)phenoxy)butyric acid;
- 30 4-(2-(9-Thiosulfatononanoylamino)phenoxy)butyric acid, sodium salt;

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- 4-(2-(8-Thiosulfatoctanoylamino)phenoxy)butyric acid,  
sodium salt;
- 4-(2-(7-Sulfiniheptanoylamino)phenoxy)butyric acid;
- 4-(2-(6-Phosphonohexanoylamino)butyric acid;
- 5 4-(2-(19-Sulfonynonadecanoylamino)phenylthio)butyric  
acid;
- 4-(2-(18-Sulfinooctadecanoylamino)phenylthio)butyric  
acid;
- 4-(2-(17-Thiosulfatoheptadecanoyl N-ethylamino)phenyl-  
10 thio)butyric acid;
- 4-(2-(16-Phosphonohexadecanoylamino)phenylthio)  
butyric acid;
- 4-(2-(14-Sulfotetradecanoylamino)phenylthio)butyric  
acid;
- 15 4-(2-(13-Sulfinotridecanoylamino)butyric acid;
- 4-(2-(12-Thiosulfatododecanoylamino)phenylthio)-  
butyric acid, salt sodium;
- 4-(2-(11-Phosphoundecanoylamino)phenylthio)butyric  
acid;
- 20 4-(2-(10-Sulfinodecanoylamino)phenylthio)butyric  
acid;
- 4-(2-(9-Carboxynonanoylamino)phenylthio)butane-  
sulfonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenylthio)butane-  
25 sulfinic acid;
- 4-(2-(7-Carboxyheptanoylamino)phenylthio)butane-  
thiosulfonic acid;
- 4-(2-(20-Carboxyeicosanoylamino)thio)phenoxy)butane-  
phosphonic acid;
- 30 4-(2-(19-Carboxynonadecanoylamino)phenoxy)butane-  
sulfonic acid;

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- 4-(2-(18-Carboxyoctadecanoyl-N-butylamino)phenoxy)-  
butane-sulfinic acid;
- 4-(2-(17-Carboxyheptadecanoylamino)phenoxy)butane-  
thiosulfonic acid;
- 5 4-(2-(15-Carboxypentadecanoylamino)phenoxy)butane-  
phosphonic acid;
- 4-(2-(14-Carboxytetradecanoylamino)phenoxy)butane-  
sulfonic acid;
- 10 4-(2-(13-n-Carboxytridecanoylamino)phenoxy)butane-  
sulfinic acid;
- 4-(2-(12-Carboxydodecanoylamino)phenoxy)butane-  
thiosulfonic acid, sodium salt;
- 4-(2-(10-Carboxydecanoylamino)phenoxy)butane-  
phosphonic acid;
- 15 4-(2-(9-Carboxynonanoylamino)phenoxy)butane-  
sulfonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenoxy)butane-  
sulfinic acid;
- 4-(2-(7-Carboxyheptanoylamino)phenoxy)butane-  
20 thiosulfonic acid, sodium salt;
- 4-(2-(20-Carboxyeicosanoylamino)phenylthio)butane-  
phosphonic acid;
- 4-(2-(19-Carboxynonadecanoyl-N-methylamino)phenyl-  
thio)butanesulfonic acid;
- 25 4-(2-(18-Carboxyoctadecanoylamino)phenylthio)butane-  
sulfonic acid;
- 4-(2-(17-Carboxyheptadecanoylamino)phenylthio)butane-  
sulfinic acid;
- 30 4-(2-(16-Carboxyhexadecanoylamino)phenylthio)butane-  
thiosulfonic acid, sodium salt;

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- 4-(2-(14-Carboxytetradecanoyl N-propylamino)phenylthio)butanephosphonic acid;
- 4-(2-(13-Carboxytridecanoylamino)phenylthio)butanesulfonic acid;
- 5 4-(2-(12-Carboxydodecanoylamino)phenylthio)butanesulfinic acid;
- 4-(2-(11-Carboxyundecanoylamino)phenylthio)butanethiosulfonic acid, sodium salt;
- 10 4-(2-(9-Carboxynonanoylamino)phenylthio)butanephosphonic acid;
- 4-(2-(8-Carboxyoctanoylamino)phenylthio)butanesulfonic acid;
- 4-(2-(7-Carboxyheptanoylamino)phenylthio)butanesulfinic acid;
- 15 4-(2-(6-Carboxyhexanoylamino)phenylthio)butanethiosulfonic acid, sodium salt;
- 3-(2-(15-Carboxyisohexadecanoylamino)phenoxy)isobutanephosphonic acid;
- 3-(2-(14-Carboxytetradecanoylamino)phenoxy)isobutanoic acid;
- 20 5-(2-(13-Carboxytridecanoylamino)phenoxy)pentanesulfinic acid;
- 5-(2-(12-Phosphonododecanoylamino)phenoxy)valeramide;
- 5-(2-(11-Sulfoundecanoylamino)valeric acid;
- 25 5-(2-(10-Sulfinodecanoyl N-methylamino)phenoxy)valeric acid;
- 5-(2-(9-Thiosulfatononanoylamino)phenoxy)valeric acid, sodium salt;
- 6-(2-(9-Phosphonononanoylamino)phenoxy)caproic acid;
- 30 6-(2-(7-Sulfoisooctanoyl-N-methylamino)phenoxy)caproic acid;

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- 7-(2-(7-Sulfiniheptanoyl-N-ethylamino)phenoxy)  
  enantic acid;  
7-(2-(6-Thiosulfatohexanoylamino)phenoxy)enanthamide,  
  sodium salt  
5 7-(2-(5-Phosphonoisohexanoylamino)phenoxy)enanthic  
  acid;  
2-(2-(11-Sulfoundecanoylamino)phenoxy)acetic  
  acid;  
2-(2-(10-Sulfodecanoyl-N-propylamino)phenoxy)acetic  
10 acid;  
3-(2-(9-Sulfinononanoylamino)phenoxy)propionic acid;  
3-(2-(12-Thiosulfatododecanoylamino)phenylthio)  
  propionamide, sodium salt;  
3-(2-(11-Phosphoundecanoylamino)phenylthio)  
15 propionic acid;  
3-(2-(11-Sulfoundecanoylamino)-4-methyl-phenylthio)  
  isobutyric acid;  
3-(2-(12-Sulfinododecanoylamino)phenylthio)  
  isobutyramide;  
20 5-(2-(11-Thiosulfoundecanoyl-N-butylamino)phenylthio)  
  valeric acid, sodium salt;  
5-(2-(10-Phosphonodecanoylamino)phenylthio)valeric  
  acid;  
5-(2-(12-Phosphonododecanoylamino)phenylthio)  
25 pentane-sulfonic acid;  
5-(2-(11-Carboxydecanoylamino)phenylthio)  
  pentane sulfinic acid;  
5-(2-(10-Phosphonodecanoylamino)phenylthio)pentane-  
  thiosulfonic acid;  
30 6-(2-(12-Phosphonododecanoylamino)phenylthio)hexane-  
  phosphonic acid;



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- 4-(2-(11-Sulfinoundecanoylamino)4-methyl-phenoxy)  
butane-thiosulfonic acid, sodium salt;
- 4-(2-(12-Sulfododecanoylamino)6-methylphenoxy)butane  
sulfonic acid;
- 5 4-(2-(11-Sulfodecanoylamino)3-chloro)phenylthio)-  
butane-sulfinic acid;
- 4-(2-(10-Sulfodecanoylamino)4-methylphenoxy)butane-  
thiosulfonic acid, sodium salt;
- 4-(2-(12-Sulfododecanoylamino)6-methylphenoxy)-  
10 butane-phosphonic acid;
- 5-(2-(11-Sulfinoundecanoylamino)-3-methylphenyl-  
thio)pentane-sulfonic acid;
- 4-(2-(11-Sulfinoundecanoylamino)-3-methylsulfonyl-  
phenoxy)butane-sulfinic acid;
- 15 4-(2-(11-Sulfinoundecanoylamino)-4-methylsulfonyl)-  
phenylthio)butanesulfonic acid;
- 4-(2-(12-Sulfinododecanoylamino)5-ethyl-phenoxy)-  
butane-phosphonic acid;
- 4-(2-(10-Sulfinodecanoylamino)-3,5-dimethylphenoxy)-  
20 butane-sulfonic acid;
- 4-(2-(9-Thiosulfatononanoylamino)-4-fluoro-phenoxy)  
butane-sulfinic acid, sodium salt;
- 4-(2-(12-Thiosulfatododecanoylamino)-5-trifluoromethyl-  
phenoxy)butane-thiosulfonic acid, sodium salt;
- 25 4-(2-(10-Thiosulfatodecanoylamino)-4-hydroxy-  
phenylthio)butane-phosphonic acid, sodium salt;
- 4-(2-(9-Phosphonononanoylamino)-3,5-dimethoxyphenyl-  
thio)butyric acid;
- 5-(2-(11-Sulfoundecanoylamino)-4-nitrophenoxy)-  
30 valeric acid;

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- 4-(2-(11-Sulfinoundecanoylamino)-5-amino-3-methyl-  
phenoxy)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-5-amino-4-methyl-  
phenylthio)butyric acid, sodium salt;
- 5 4-(2-(12-Phosphonododecanoylamino)-4-dimethyl-amino-  
phenoxy)butyric acid;
- 4-(2-(10-Sulfodecanoylamino)-phenoxy)butyric acid;
- 3-(2-(9-Sulfinononanoylamino)phenoxy)propionic acid;
- 3-(2-(12-Thiosulfatododecanoylamino)phenoxy)-3-methyl-  
10 propionic acid, sodium salt;
- 3-(2-(11-Phosphonodecanoylamino)thienyloxy)-2-chloro-  
propionic acid;
- 4-(2-(9-Sulfononanoylamino)thienyloxy-3-ethoxy-  
butyric acid;
- 15 4-(2-(12-Sulfinododecanoylamino)phenoxy)-2-fluoro-  
butyric acid;
- 7-(2-(11-Thiosulfatoundecanoylamino)phenoxy)6-amino-  
enanthic acid, sodium salt;
- 5-(2-(11-Phosphonoundecanoylamino)-3-methylphenoxy)-4-  
20 oxo-valeric acid;
- 4-(2-12-Sulfododecanoylamino)phenoxy)but-2-enoic  
acid;
- 4-(2-(11-Sulfinodecanoylamino)phenoxy)but-2-enoic  
acid;
- 25 4-(2-(10-Thiosulfatodecanoylamino)phenoxy)-4-methyl-  
ene valeric acid, sodium salt;
- 4-(2-(9-Phosphonononanoylamino)phenoxy)-4-fluoro-2-  
butenoic acid;
- 4-(2-(11-Sulfo-3-methylbutanoylamino)thienyloxy)-  
30 butyric acid;

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- 4-(2-(4-Sulfinio-3-chlorobutanoylamino)thienyloxy)-  
butyric acid;
- 4-(2-(9-Thiosulfato-2-methoxynonanoylamino)thienyl-  
oxy)butyric acid, sodium salt;
- 5 4-(2-(4-Phosphono-2-ethoxybutanoylamino)phenoxy)  
butyric acid;
- 4-(2-(14-Sulfo-14-fluoro-2-acetamidotetradecanoyl-  
amino)-3-methylphenoxy)butyric acid;
- 4-(2-(13-Sulfinio-2-oxotridecanoylamino)-4-methylthio)-  
10 phenyloxy)butyric acid;
- 4-(2-(12-Thiosulfatododecanoyl-3-en-amino)phenoxy)  
butyric acid;
- 4-(2-(11-Phosphonoundecanoyl-7-ene-amino)phenoxy)  
butyric acid;
- 15 4-(2-(4-Sulfo-2-fluoro-2-butenoylamino)phenoxy)-  
butyric acid;
- 4-(2-(12-Sulfinododecanoylamino)-4-methyl-3-pyridyl-  
oxy)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-4-methyl-3-  
20 pyridyloxy)butyric acid;
- 4-(2-(10-Phosphonodecanoylamino)-5-methyl-3-  
pyridyloxy)butyric acid;
- 4-(2-(11-Sulfinodecanoylamino)-4-nitro-3-pyridylthio-  
butyric acid;
- 25 4-(2-(10-Thiosulfatodecanoylamino)-6-methylsulfonyl-3-  
pyridyloxy)butyric acid, sodium salt;
- 4-(2-(9-Phosphonononanoylamino)5-chloro-3-pyridyl-  
thio)butyric acid;
- 4-(2-(11-Sulfoundecanoylamino)5-methylsulfonyl-3-  
30 pyridylthio)butyric acid;

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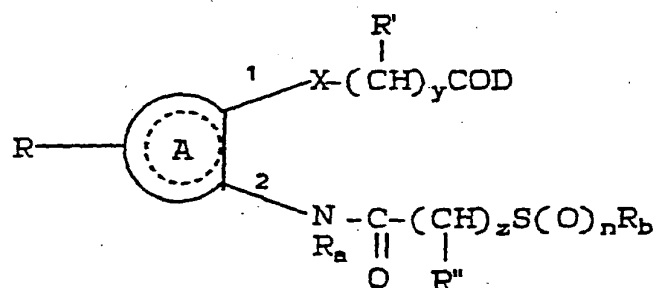
- 4-(2-(11-Sulfinoundecanoylamino)-6-methyl-3-pyridylthio)butyric acid;
- 4-(2-(11-Thiosulfatoundecanoylamino)-4,6-dimethyl-3-pyridyloxy)butyric acid, sodium salt;
- 5 4-(2-(12-Phosphonododecanoylamino)-5-(methylthio)-3-pyridyloxy)butyric acid;
- 4-(2-(10-Sulfodecanoylamino)-5-methoxy-3-pyridyloxy)butyric acid;
- 10 4-(2-(9-Sulfinononanoylamino)-4-fluoro-6-methyl-3-pyridyloxy)butyric acid;
- 4-(2-(12-Thiosulfatododecanoylamino)-5-(methylamino)-3-pyridyloxy)butyric acid, sodium salt;
- 4-(2-(11-Phosphonoundecanoylamino)-4-phenyl-3-pyridylthio)butyric acid;
- 15 4-(2-(9-Sulfononanoylamino)-6-methoxy-3-pyridylthio)butyric acid;
- 4-(2-(12-Sulfinododecanoylamino)-6-trifluoromethyl-3-pyridyloxy)butyric acid;
- 20 5-(2-(11-Thiosulfatoundecanoylamino)-4-methyl-3-thiophenyloxy)valeric acid, sodium salt;
- 4-(2-(11-Phosphonoundecanoylamino)-4-methyl-3-thiophenyloxy)butyric acid;
- 4-(2-(12-Sulfododecanoylamino)-5-methyl-3-thiophenylthio)butyric acid;
- 25 4-2-(2-(11-Sulfinoundecanoylamino)-4-methyl-3-thiophenylthio)butyric acid;
- 4-(2-(10-Thiosulfatodecanoylamino)-5-methyl-3-thienylthio)butyric acid, sodium salt;
- 30 4-(2-(9-Phosphonononanoylamino)-4-hydroxy-3-thienyloxy)butyric acid;

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- 4-(2-(11-Sulfodecanoylamino)-4-methylthio-3-thienyloxy)butyric acid;  
4-(2-(10-Sulfinodecanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid;  
5 4-(2-(9-Thiosulfatononanoylamino)-4-methylsulfonyl-3-thienyloxy)butyric acid, sodium salt;  
4-(2-(12-Phosphonododecanoylamino)-5-trifluoromethyl-3-thienyloxy)butyric acid;  
10 4-(2-(11-Sulfoundecanoylamino)-4-methyl-5-phenyl-3-thienyloxy)butyric acid;  
4-(2-(11-Sulfinoundecanoylamino)-5-methylamino-3-thienyloxy)butyric acid;  
4-(2-(12-Thiosulfatododecanoylamino)-5-dimethylamino-3-thienyloxy)butyric acid, sodium salt;  
15 4-(2-(11-Phosphoundecanoylamino)-4-amino-3-thienyloxy)butyric acid;  
Preferred compounds in the invention include:  
4-(2-(11-Carboxyundecanoylamino)phenoxy)butyric acid,  
4-(2-(11-Carboxyundecanoylamino)phenylthio)butyric  
20 acid,  
4-(2-(9-Carboxynonanoylamino)phenoxy)butyric acid,  
4-(2-(10-Carboxydecanoylamino)phenoxy)butyric acid,  
4-(2-(12-Carboxydodecanoylamino)phenoxy)butyric acid,  
4-(2-(13-Carboxytridecanoylamino)phenoxy)butyric acid,  
25 4-(2-(15-Carboxypentadecanoylamino)phenoxy)butyric acid,  
4-(2-(11-Carboxyundecanoylamino)-4-methylphenoxy)-butyric acid,  
4-(2-(11-Carboxyundecanoylamino)-5-methylphenoxy)-  
30 butyric acid.

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Also included as a 5 $\alpha$ -reductase inhibitor in this invention is an agent of the following formula:



wherein

A is an 1,2-disubstituted aromatic ring, preferably a benzene ring;

D is OH, NH<sub>2</sub>, NHR<sub>C</sub>, OR<sub>C</sub>;

X is O, S, SO, or SO<sub>2</sub>;

R is H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

phenyl or substituted phenyl,

halo,

haloalkyl,

hydroxy,

carboxy,

cyano,

C<sub>1</sub>-C<sub>4</sub> alkoxy,

C<sub>1</sub>-C<sub>4</sub> alkylthio,

C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,

C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl,

nitro,

amino,

C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;

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R' and R'' are independently

H,

halo,

C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,

5 amino, or oxo, where CH-R' or CH-R''

in the formula become -C=O;

R<sub>a</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl;

10 R<sub>b</sub>, R<sub>c</sub> are independently, C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl,  
phenyl-C<sub>1</sub>-C<sub>4</sub> alkyl;

n is 0-2;

15 y is 1-6;

z is 6-20; and

wherein

20  $\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array}$  and

$\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array}$  can independently represent substituted or  
unsubstituted alkyl radicals or alkenyl radicals  
containing at least one alkene bond;

25 and pharmaceutically acceptable salts and esters  
thereof.

The compounds of the instant invention are  
inhibitors of the human testosterone 5 $\alpha$ -reductase.

30 The scope of the compounds of the instant  
invention are described by the above-described  
formula.

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In the description of the formula the following terms are used which are hereby defined:

X can be O or S, preferably one X being O, and particularly preferred wherein both Xs are O, i.e., the catechol structure.

"C<sub>1</sub>-C<sub>4</sub> alkyl" includes linear or branched species, e.g. methyl, ethyl, n-propyl, isopropyl, cyclopropyl, n-butyl, isobutyl, sec-butyl, t-butyl; and "C<sub>1</sub>-C<sub>12</sub> alkyl" includes alkyl up to 12 carbons including n-octyl, t-decyl, n-dodecyl.

"Phenyl C<sub>1</sub>-C<sub>4</sub> alkyl" includes benzyl, 2-phenethyl, and the like;

"C<sub>1</sub>-C<sub>4</sub> alkoxy" includes linear or branched species, e.g., methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy, t-butoxy;

"Halo" includes fluoro, chloro, bromo or iodo;

"Substituted phenyl" includes phenyl substituted by one or more of C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy, or halo, and the like, as defined above; representative examples include o, m-, p-methoxy phenyl; 2,4-dimethoxyphenyl; 2-chloro-4-ethoxyphenyl; 3,5-dimethoxyphenyl; 2,4-dichlorophenyl; 2-bromo-4-methylphenyl, o-fluorophenyl, and the like.

"Haloalkyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with one or more "halo" as defined above and includes: trifluoromethyl, 2,2-dichloroethyl and the like.

"C<sub>1</sub>-C<sub>4</sub> alkylthio" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one divalent thio (-S-) grouping including; methylthio, ethylthio, isopropylthio, n-butylthio, and the like.



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"C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one -SO- grouping including; methylsulfinyl, ethylsulfinyl; isopropylsulfinyl, and the like.

5 "C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl" includes C<sub>1</sub>-C<sub>4</sub> alkyl, defined above, substituted with at least one sulfonyl group, -SO<sub>2</sub>-, including; methylsulfonyl, ethylsulfonyl, isopropylsulfonyl, n-butylsulfonyl, and the like;

10 "C<sub>1</sub>-C<sub>4</sub> mono or dialkyl amino" includes amino, substituted with one or more C<sub>1</sub>-C<sub>4</sub> alkyl groups as defined hereinabove, including: methylamino, ethylamino, n-butylamino, t-butylamino, dimethylamino, N,N-diethylamino, methyl-t-butylamino, and the like.

15 The R group or groups on the benzene ring can be present initially in the process, e.g. phenyl, methyl, methoxy, cyano, carbomethoxy, trifluoromethyl, (present as in the starting 6-nitrophenol 1 in Flow Chart A) or added later by a  
20 conventional reaction, e.g. chloro, as by chlorination, nitro by nitration, or created from a starting or added functional group present, e.g. converting a later added nitro to an amino group by catalytic reduction, then alkylating to a mono or  
25 dialkylamine. An amino group can be subjected to diazotization to a hydroxy group, which can be followed by methylation to a methoxy group. Similarly, a hydroxy group can be converted to a thiol by the analogous procedures described in J.  
30 Org. Chem. 31, pp 3980-3984 (1966) by Newman and Karnes, and J. Org. Chem. 31, pp 410 (1966) by Kwart, H. and Evans, E.S. The resulting thiol can be

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alkylated to alkylthio, which can be oxidized to the corresponding sulfoxide or sulfone. Preferred substituents are H, C<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkoxy and phenyl. These reactions and sequences are conventional in the art and it will be obvious to one skilled in the art to modify the benzene ring to arrive at an R radical disclosed herein.

By the term "pharmaceutically acceptable salts and esters thereof" is meant salts and esters of the acid groups in the final molecule which can be used as part of the human drug delivery system and include the salts: sodium, potassium, calcium, ammonium, substituted ammonium, quaternary ammonium, and esters: ethyl ester, acetate, besylate, edetate, phenpropionate, acetate, pamoate, and esters which serve as "prodrug" formulations which will hydrolyze in the body at physiological pH's to regenerate the acid, including pivaloylates, e.g. pivoxetil and pivoxil, and Kanebo esters, and the like.

(CH)<sub>y</sub>, where y is 1-6, preferably 3, can contain at least one R' substituent as defined above, and can be, e.g., -CH<sub>2</sub>-; -CH<sub>2</sub>-CH<sub>2</sub>-; -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-; -CH-; -CH-CH<sub>2</sub>-; -CH<sub>2</sub>-CH-; -CH<sub>2</sub>-CH-CH<sub>2</sub>-; -CH<sub>2</sub>-CH-CH<sub>2</sub>-;  $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}_2-\text{CH}_2-\text{CH}- \end{array}$ ;  $\begin{array}{c} \text{CH}_3 \\ | \\ -\text{CH}_2-\text{CH}- \end{array}$ ;  $\begin{array}{c} \text{Cl} \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2- \end{array}$ ;  $\begin{array}{c} \text{OCH}_3 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2- \end{array}$ ;  $\begin{array}{c} \text{OCH}_2\text{CH}_3 \\ | \\ -\text{CH}_2-\text{CH}-\text{CH}_2- \end{array}$ ;  $\begin{array}{c} \text{F} \\ | \\ -\text{CH}_2-\text{CH}_2-\text{CH}- \end{array}$ ; and the like.

30

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An alkene bond can also be present in

$\begin{array}{c} R' \\ | \\ (CH)_y \end{array}$ , e.g.,  $CH_2-CH=CH-$ ;  $CH_2-CH=CH-CH_2-$ ;  $-CH_2-CH=CH-$ ;  $-(CH_2)_3-CH=CH-$  and the like.

5

$\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$ , where z is 6-20, preferably 8-14, can contain at least one R'' substituent as defined above, and can be completely alkyl; e.g.,  $(CH_2)_n-COOH$ , where n is 8-14 preferably and the like.

10

An alkene bond can also be present in

$\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$ , e.g.,  $-(CH_2)_4-CH=CH-(CH_2)_4-$ , and the like.

15

Preferred is where one R' or R'' is H and

particularly preferred is where both  $\begin{array}{c} R' \\ | \\ (CH)_y \end{array}$  and  $\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$  are alkyl.

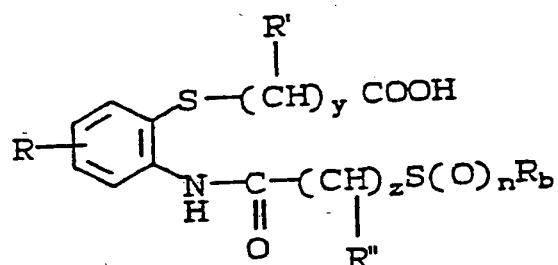
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Preferred compounds of the instant invention are given by the following formulas;

25

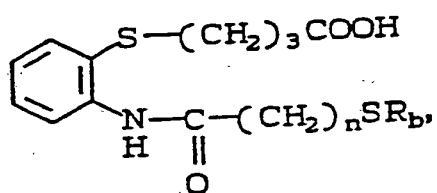
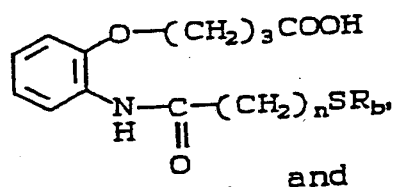
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wherein R, R', R'', Y, Z, R<sub>b</sub> are defined above;

and particularly preferred are:



where n is 8-14, and R<sub>b</sub> is methyl, ethyl, cyclopropyl, isopropyl, n-propyl, t-butyl, phenyl or benzyl.

The compounds of the instant invention can be made by the procedures outlined in the following Flowcharts.

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## FLOW CHART A-3

5

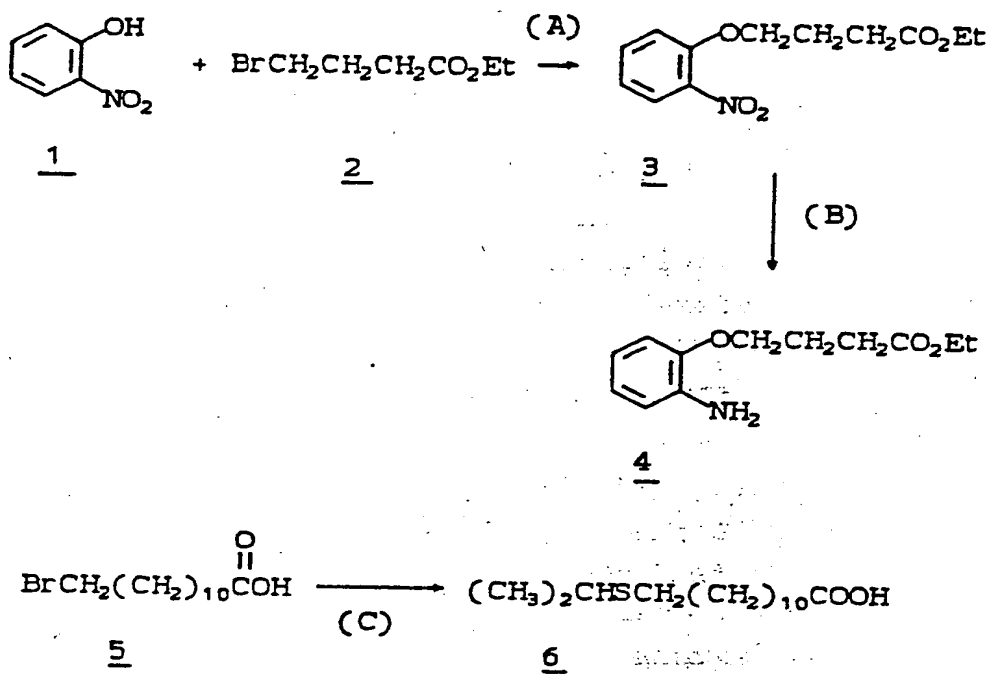
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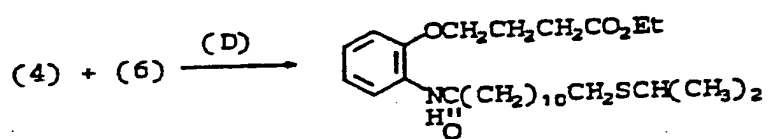
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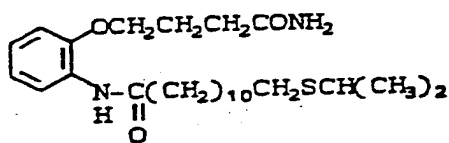
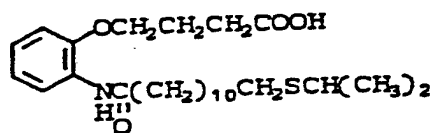
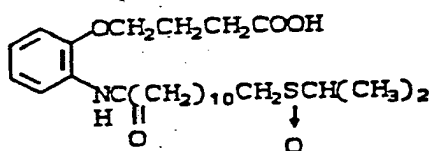
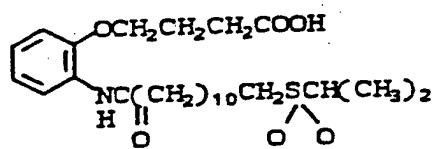
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## FLOW CHART A-3 CONT'D.

7

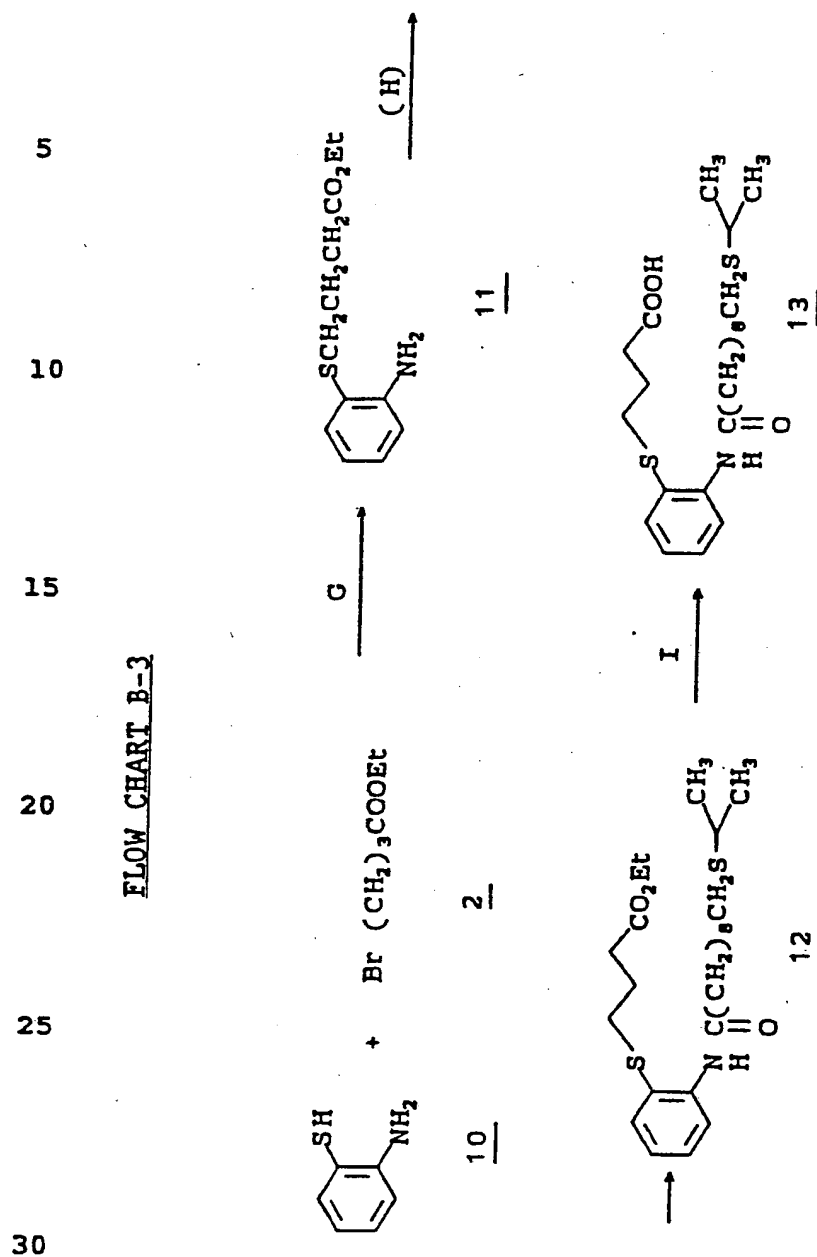
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(E)

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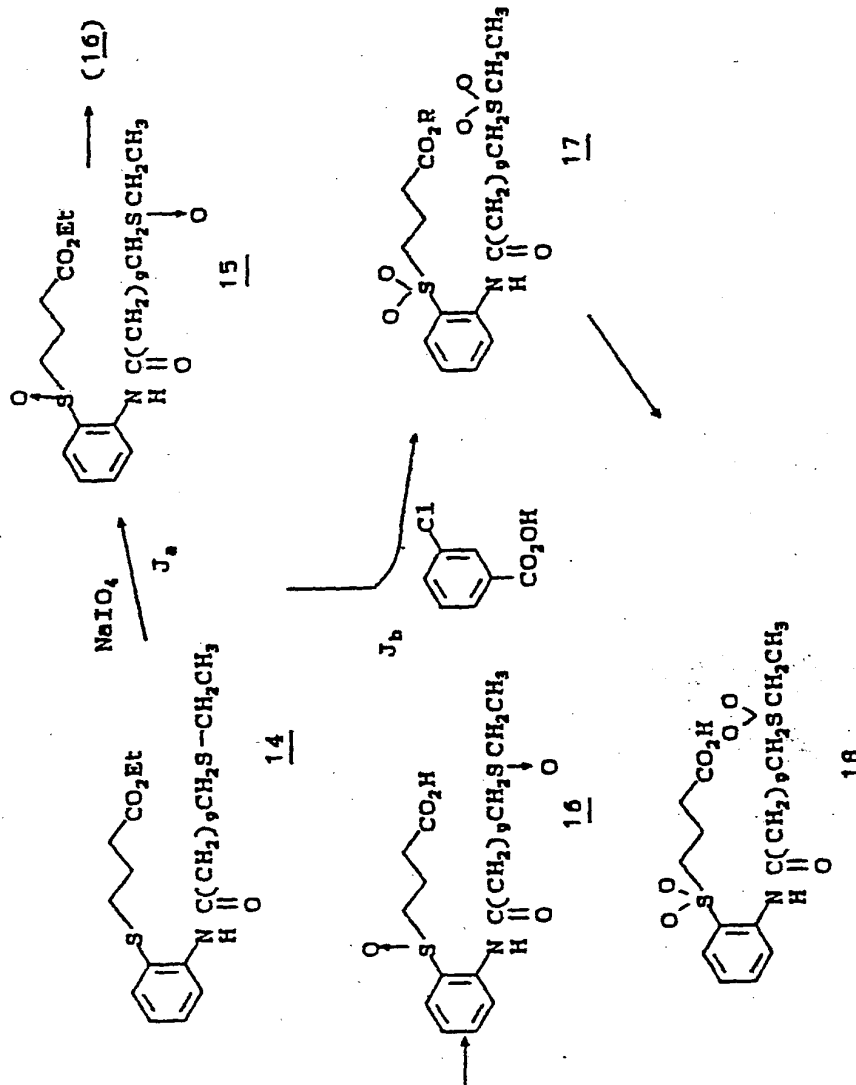
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## FLOW CHART B-3



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## FLOW CHART C-3





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As seen in Flow Chart A-3, o-nitrophenol 1, ethyl 4-bromobutyrate 2 and anhydrous  $K_2CO_3$  in e.g., dry acetone are heated at reflux e.g. for 12-100 hours, or stirred for an extended period of time at room temperature, under a nitrogen atmosphere to product ethyl 4-(2-nitrophenoxy) butyrate 3, in Step (A).

A solution of 3 in e.g., ethyl acetate is catalytically hydrogenated at room temperature under e.g. 40 psig of  $H_2$  in the presence of a 5% Pd/C catalyst to yield ethyl 4-(2-aminophenoxy)butyrate 4 in Step (B).

Step (C) comprises reacting the 12-bromo dodecanoic acid 5 with isopropyl mercaptan in a suitable solvent, e.g., dimethoxyethane, at about 80-85°C to obtain the acid 6.

In Step (D) the mono acid 6 is reacted with the amine 4 and N'N'-dicyclohexylcarbodiimide (DCC) at e.g., room temperature in e.g., dry methylene chloride, optionally in the presence of 4-dimethylaminopyridine, to produce the amide 7.

In Step (E), the ether-amide 7 is de-esterified by e.g., 2.5 N NaOH in MeOH/ $H_2O$  to yield the final product, monoacid 8.

The monoacid 8 can be treated with  $NaIO_4$  in (acetone/water) at room temperature for (4-24 hours) to produce the corresponding sulfoxide 8a. Additionally, 8 can be treated with meta-chlorobenzoic acid in ( $CH_2Cl_2$ ) at a temperature of about 0° to 25°C for (1-24 hours) to produce the corresponding sulfone 8b.

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In Step (F) the ester 7 is treated with ammonia in (methanol) at room temperature for, e.g., 1-7 days to produce the amide 9.

5 Flow Chart B-3 illustrates the synthesis of the sulfur analogs of the invention compounds.

In Step G, the orthoaminothiophenol is reacted with the bromoester 2 under conditions similar to Step A to produce the thioether 11.

10 In Step (H), the thioether 11 is reacted with an alkylthioalkanoic acid under similar conditions using DCC analogously as in Step D to produce the acylated ester 12.

15 In Step I, the ester 12 is hydrolyzed to produce the free thio acid 13, which has the 5- $\alpha$ -reductase activity described herein.

20 As seen in Flow Chart C-3, the compound 13 can further be oxidized to the sulfoxide in Step J<sub>a</sub>, starting with the thio compound 14 to produce the sulfoxide 15, which can be hydrolyzed, analogous to the conditions in Step I to produce the active acid 16.

25 In a similar manner, 14 can be converted to the sulfone-ester 17, which can then be hydrolyzed analogous to the conditions in Step I to the corresponding acid 18.

30 Alternatively, the sulfur in o-nitrobenzene thiol as a separate starting material analogous to 1, can be coupled to yield the ester alkylthio compound corresponding to 3 which can be oxidized to the corresponding sulfoxide or sulfone, then followed by reduction of the nitro group to the amino and then

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coupled with a suitable reagent e.g., 6, to yield the linear amide containing unoxidized sulfur analogous to 7. A further modification is where the sulfuracylating agent is first oxidized to the  
5 corresponding sulfoxide or sulfone, then coupled with the amino group of e.g., 11 to yield e.g. 13 containing only an oxidized sulfur in the amide chain.

It is obvious that other nitrophenols can be substituted for 1 in Flow Chart A-3 to provide the  
10 scope of the compounds covered by this invention and include the following:

2-nitrophenol  
2-nitro-6-methylphenol  
15 2-nitro-5-methylphenol  
2-nitro-4-methylphenol  
2-nitro-3-methylphenol  
2-nitro-4-phenylphenol  
2-nitro-5-phenylphenol  
20 2-nitro-4-chlorophenol  
2-nitro-4-(trifluoromethyl)phenol  
2-nitro-4-methoxyphenol  
2-nitro-6-ethoxyphenol, and the like.

25 Starting materials for Flow Charts B-3 and C-3 in addition to 10 are commercially available and readily made by prior art procedures and include all of the above listed compounds where - SH is substituted for -OH, ortho to the nitro group.

30

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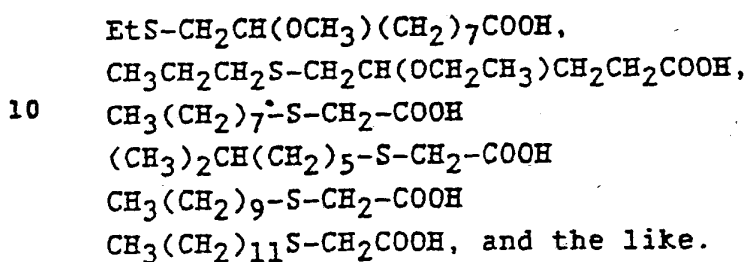
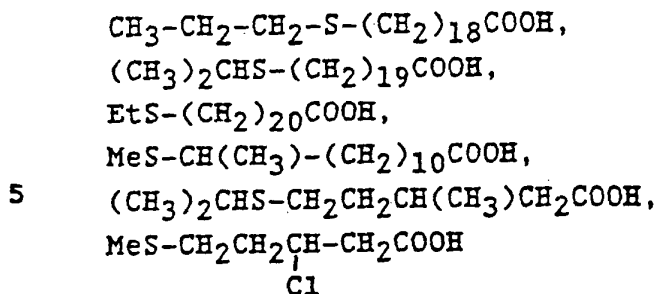
Other starting materials for 2 in both Flow Charts A-3 and B-3 include the following:

- 5           Br-CH<sub>2</sub>-COOMe,  
           Cl-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOCH(CH<sub>3</sub>)<sub>3</sub>,  
           Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOMe,  
           Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOEt,  
           Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>,  
           Br-CH<sub>2</sub>CH(CH<sub>3</sub>)COOMe,  
 10          Br-CH<sub>2</sub>CH(CH<sub>3</sub>)CH<sub>2</sub>COOEt,  
           Br-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>COOMe,  
           Br-CH<sub>2</sub>CH(OCH<sub>3</sub>)CH<sub>2</sub>COOCH(CH<sub>3</sub>)<sub>2</sub>,  
           Cl-CH<sub>2</sub>CH(OCH<sub>2</sub>CH<sub>3</sub>)CH<sub>2</sub>COOMe,  
           Br-CH<sub>2</sub>CH(F)CH<sub>2</sub>COOMe,  
 15          and the like.

Other starting materials for the acid 6 to produce the acid for acylating the amino group in 4 or 11 include the following:

- 20           MeS-(CH<sub>2</sub>)<sub>6</sub>COOH,  
           MeS-(CH<sub>2</sub>)<sub>7</sub>COOH,  
           (CH<sub>3</sub>)<sub>2</sub>CHS-(CH<sub>2</sub>)<sub>8</sub>COOH,  
           EtS-(CH<sub>2</sub>)<sub>9</sub>COOH,  
 25          CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>S(CH<sub>2</sub>)<sub>10</sub>COOH,  
           (CH<sub>3</sub>)<sub>2</sub>CHS(CH<sub>2</sub>)<sub>11</sub>COOH,  
           MeS-(CH<sub>2</sub>)<sub>12</sub>COOH,  
           EtS-(CH<sub>2</sub>)<sub>13</sub>COOH,  
           CH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>S-(CH<sub>2</sub>)<sub>14</sub>COOH,  
 30          (CH<sub>3</sub>)<sub>2</sub>CHS-(CH<sub>2</sub>)<sub>15</sub>COOH,  
           CH<sub>3</sub>(CH<sub>2</sub>)<sub>3</sub>S-(CH<sub>2</sub>)<sub>16</sub>COOH,  
           (CH<sub>3</sub>)<sub>2</sub>CH-CH<sub>2</sub>S-(CH<sub>2</sub>)<sub>17</sub>COOH,

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- 15 Representative compounds of the instant invention include, but are not limited to:  
 4-(2-(20-Isopropylthioeicosanoylamino)phenoxy)butyric acid;  
 4-(2-(19-Methylthiononadecanoylamino)phenoxy)butyric  
 20 acid;  
 4-(2-(18-Ethylthioloctadecanoylamino)phenoxy)butyric acid;  
 4-(2-(17-Isopropylthioheptadecanoylamino)phenoxy)-  
 butyric acid;  
 25 4-(2-(16-Methylthiohexadecanoylamino)phenoxy)butyric acid;  
 4-(2-(15-Methylsulfinylpentadecanoylamino)phenoxy)-  
 butyric acid;  
 4-(2-(14-Methylsulfinyltetradecanoylamino)phenoxy)-  
 30 butyric acid;  
 4-(2-(13-n-Propylthiotridecanoylamino)phenoxy)-  
 butyric acid;

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- 4-(2-(12-n-Butylsulfinyldodecanoylamino)phenoxy)-  
butyric acid;
- 4-(2-(11-sec-Butylthioundecanoylamino)phenoxy)-  
butyric acid;
- 5 4-(2-(10-phenylthiodecanoylamino)phenoxy)-butyric  
acid;
- 4-(2-(10-benzylthiodecanoylamino)phenoxy)-butyric  
acid;
- 10 4-(2-(10-iso-Butylsulfonyldecanoylamino)phenoxy)-  
butyric acid;
- 4-(2-(9-t-Butylthiononanoylamino)phenoxy)butyric  
acid;
- 4-(2-(8-Ethylsulfonyloctanoamino)phenoxy)butyric acid;
- 4-(2-(7-Isopropylthioheptanoylamino)phenoxy)butyric  
15 acid;
- 4-(2-(6-Methylthiohexanoylamino)butyric acid;
- 4-(2-(20-Ethylsulfonyleicosanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(19-Isopropylthiononadecanoylamino)phenylthio)-  
20 butyric acid;
- 4-(2-(18-Methylthiooctadecanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(17-Ethylthioheptadecanoylamino)phenylthio)-  
butyric acid;
- 25 4-(2-(16-Isopropylhexadecanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(15-Methylthiopentadecanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(14-Methylsulfinyltetradecanoylamino)phenylthio)-  
30 butyric acid;
- 4-(2-(13-Methylsulfonyltridecanoylamino)butyric acid;

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- 4-(2-(12-n-Propylthiododecanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(11-n-Butylsulfinylundecanoylamino)phenylthio)-  
butyric acid;
- 5 4-(2-(10-sec-Butylthiododecanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(10-phenylthiododecanoylamino)phenylthio)-butyric  
acid;
- 10 4-(2-(10-benzylthiododecanoylamino)phenylthio)-butyric  
acid;
- 4-(2-(9-iso-Butylsulfonylnonanoylamino)phenylthio)-  
butyric acid;
- 4-(2-(8-t-Butylthiooctanoylamino)phenylthio)butyric  
acid;
- 15 4-(2-(7-Ethylsulfinylheptanoylamino)phenylthio  
butyric acid;
- 4-(2-(6-Isopropylthiohexanoylamino)phenylthio  
butyric acid;
- 20 3-(2-(16-Methylsulfinylhexadecanoylamino)phenoxy)-  
propionic acid;
- 4-(2-(15-Methylsulfonylisohexadecanoylamino)phenoxy)-  
butyric acid;
- 3-(2-(14-n-Propylthiotetradecanoylamino)phenoxy)-  
isobutyric acid;
- 25 5-(2-(13-n-Butylsulfinyltridecanoylamino)phenoxy)-  
valeric acid;
- 5-(2-(12-sec-Butylthiododecanoylamino)phenoxy)-  
valeric acid;
- 5-(2-(11-iso-Butylsulfonylisododecanoylamino)-  
valeric acid;
- 30 5-(2-(11-t-Butylthioundecanoylamino)valeric acid;
- 5-(2-(10-Ethylsulfinyldecanoylamino)valeric acid;

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- 5-(2-(9-Isopropylthiononanoylamino)phenoxy)valeric acid;
- 6-(2-(9-Methylthiononanoylamino)phenoxy)caproic acid;
- 6-(2-(8-Ethylthiooctanoylamino)phenoxy)caproic acid;
- 5 6-(2-(7-Isopropylthioisooctanoylamino)phenoxy)caproic acid;
- 7-(2-(7-Methylheptanoylamino)phenoxy)enanthic acid;
- 7-(2-(6-Methylsulfinylhexanoylamino)phenoxy)enanthic acid;
- 10 7-(2-(5-Methylsulfonylisoheptanoylamino)phenoxy)-enanthic acid;
- 2-(2-(12-n-Propylthiododecanoylamino)phenoxy))acetic acid;
- 2-(2-(11-n-Butylsulfinylundecanoylamino)phenoxy)acetic acid;
- 15 2-(2-(10-sec-Butylthiodecanoylamino)phenoxy)acetic acid;
- 3-(2-(9-iso-Butylsulfonylnonanoylamino)propionic acid;
- 20 3-(2-(12-t-Butylthiododecanoylamino)phenylthio)-propionic acid;
- 3-(2-(11-Ethylsulfinylundecanoylamino)phenylthio)-propionic acid;
- 4-(2-(11-Isopropylthioundecanoylamino)phenylthio)-butyric acid;
- 25 4-(2-(11-Methylthioundecanoylamino)-4-methyl-thio-phenoxy)butyric acid;
- 4-(2-(12-Ethylthiododecanoylamino)phenylthio)-butyric acid;
- 30 5-(2-(11-Isopropylthioundecanoylamino)phenylthio)-valeric acid;



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- 5-(2-(10-Methylthiodecanoylamino)phenylthio)valeric acid;
- 5-(2-(9-Methylsulfinylnonanoylamino)phenylthio)-valeric acid;
- 5 5-(2-(12-Methylsulfonyldodecanoylamino)phenylthio)-valeric acid;
- 5-(2-(11-n-Propylthiodecanoylamino)phenylthio)-valeric acid;
- 10 5-(2-(10-n-Butylsulfinyldecanoylamino)phenylthio)-valeric acid;
- 6-(2-(9-sec-Butylthiononanoylamino)phenoxy)caproic acid;
- 6-(2-(12-iso-Butylsulfonyldodecanoylamino)phenylthio)caproic acid;
- 15 6-(2-(11-t-Butylthioundecanoylamino)phenylthio)-caproic acid;
- 7-(2-(11-Ethylsulfinylundecanoylamino)-3-methylphenylthio)enanthic acid;
- 7-(2-(11-Isopropylthioundecanoylamino)-4-methylphenylthio)enanthic acid;
- 20 7-(2-(12-Methylthiododecanoylamino)phenoxy)enanthic acid;
- 4-(2-(11-Phenylthioundecanoylamino)4-methyl-phenoxy)-butyric acid;
- 25 4-(2-(10-Benzylthiodecanoylamino)3-methylphenoxy)-butyric acid;
- 4-(2-(9-Methylthiononanoylamino)5-methylphenoxy)-butyric acid;
- 4-(2-(12-Methylsulfinyldecanoylamino)6-methylphenoxy)butyric acid;
- 30 4-(2-(11-Methylsulfonyldecanoylamino)3-phenylthio)butyric acid;

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- 4-(2-(10-n-Propylthiodecanoylamino)4-methylphenoxy)-  
butyric acid;
- 4-(2-(9-n-Butylsulfinylnonanoylamino)5-fluoromethyl-  
phenylthio)butyric acid;
- 5 4-(2-(12-sec-Butylthiododecanoylamino)6-methyl-  
phenoxy)butyric acid;
- 5-(2-(11-iso-Butylsulfonylundecanoylamino)-3-methyl-  
phenylthio)valeric acid;
- 10 4-(2-(11-t-Butylthioundecanoylamino)-3-methylsul-  
fonylphenoxy)butyric acid;
- 4-(2-(11-Ethylsulfinylundecanoylamino)-4-methyl-  
sulfonylphenylthio)butyric acid;
- 4-(2-(12-Isopropylthiododecanoylamino)5-ethyl-  
phenoxy)butyric acid;
- 15 4-(2-(11-Methylthioundecanoylamino)4-phenylphenoxy)-  
butyric acid;
- 4-(2-(10-Ethylthiodecanoylamino)-3,5-dimethylphenoxy)-  
butyric acid;
- 4-(2-(9-Isopropylthiononanoylamino)-4-fluoro-phenoxy)-  
20 butyric acid;
- 4-(2-(12-Methylthiododecanoylamino)-5-trifluoromethyl-  
phenoxy)butyric acid;
- 4-(2-(11-Isopropylthio)undecanoylamino)phenoxy)butyric  
25 acid,
- 4-(2-(11-Ethylthio)undecanoylamino)phenylthio)butyric  
acid,
- 4-(2-(9-Isopropylthio)nonanoylamino)phenoxy)butyric  
acid,
- 30 4-(2-(10-Isopropylthio)decanoylamino)phenoxy)butyric  
acid,

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4-(2-(12-Isopropylthio)dodecanoylamino)phenoxy)butyric acid,

4-(2-(13-Butylthio)tridecanoylamino)phenoxy)butyric acid,

5 4-(2-(15-t-Butylthio)pentadecanoylamino)phenoxy)butyric acid,

5-(2-(11-Isopropylthio)undecanoylamino)phenoxy)valeric acid,

10 4-(2-(11-Ethylsulfinyl)undecanoylamino)-phenoxy)butyric acid,

4-(2-(11-Isopropylsulfonyl)undecanoylamino)-4-methylphenoxy)butyric acid,

4-(2-(11-Ethylsulfinyl)undecanoylamino)-5-methylphenoxy)butyric acid.

15 All of the compounds described above in the present invention, prepared in accordance with the methods described above, are, as already described, can be used to treat BPH in combination with an  
20 aromatase inhibitor, by oral, parenteral or topical administration.

In this invention, the aromatase inhibitor, and the 5 $\alpha$ -reductase inhibitor are administered in combination separately or as one single combined  
25 pharmaceutical composition via parenteral or oral means. Preferably the aromatase inhibitor and the 5 $\alpha$ -reductase inhibitor are administered orally as separate compositions.

30

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5       The amount of each component administered is determined by the attending clinicians taking into consideration the etiology and severity of the disease, the patient's condition and age, the potency of each component and other factors.

10       The aromatase inhibitor compositions are generally administered in a dosage range of about 10 to 400 mg/kg (body weight) per day with 50 to 250 mg per day in a single dose being preferred.

15       The 5 $\alpha$ -reductase inhibitor compositions are generally administered in a dosage range of about 0.01 to 1.0 mg/kg (body weight) per day with one to 70 mg per day in one daily total dose being preferred.

20       In the preferred aspect of this invention, the aromatase inhibitor is fadrazole which is administered orally in a daily dose of about 100 mg/kg. and the 5 $\alpha$ -reductase inhibitor is finasteride, which is administered orally in a daily dose of about 10 mg/kg.

25       The aromatase inhibitor and the 5 $\alpha$ -reductase inhibitor may be compounded into a single dosage form suitable for oral or parenteral administration. A tablet or capsule or caplets are particularly convenient forms for oral administration. Such compositions useful in the present invention are typically formulated with conventional pharmaceutical excipients, e.g., spray dried lactose and magnesium stearate into  
30       tablets or capsules for oral administration. One or

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more of the active substances, with or without additional types of active agents, can be worked into tablets or dragee cores by being mixed with solid, pulverulent carrier substances, such as sodium  
5 citrate, calcium carbonate or dicalcium phosphate, and binders such as polyvinyl pyrrolidone, gelatin or cellulose derivatives, possibly by adding also lubricants such a magnesium stearate, sodium lauryl sulfate, "Carbowax" or polyethylene glycols. Of  
10 course, taste improving substances can be added in the case of oral administration forms.

As further forms of administration, one can use plug capsules, e.g. hard gelatin, as well  
15 as closed softgelatin capsules comprising a softener or plasticizer, e.g. glycerine. The plug capsules contain the active substance preferably in the form of a granulate, e.g. in mixtures with fillers, such as lactose, saccharose, mannitol, starches such as  
20 potato starch or amylopectin, cellulose derivatives or highly-dispersed silicic acids. In soft gelatin capsules, the active substance is preferably dissolved or suspended in suitable liquids, such as vegetable oils or liquid polyethylene glycols.

25  
The active ingredient components used in accordance with the present invention may also be formulated into once-a-day or even longer sustained release composition by conventional techniques well  
30 known in the art.

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In place of oral administration, the active compounds may be administered parenterally. In such case, one can use a solution of the active substance, e.g., in sesame oil or olive oil.

5

Following the above treatment using the described regimen, the symptoms of BPH including enlarged prostate volume, nocturia, increased hesitancy, decreased urinary flow, are inhibited, in some cases prevented when treating androgen-dependent diseases such a benign prostatic hypertrophy in accordance with this invention.

10

To assist in determining the effect of the prostatic treatment, blood plasma concentration of testosterone (T), dihydrotestosterone (DHT), estradiol and prostate acid phosphatase (PAP) as well as prostate volume, urinary flow rate, hesitancy and nocturia are measured. Lowered concentrations of DHT, estradiol, prostatic PAP and reduction in prostate volume, are indicative of successful treatment. The concentrations of the above-listed components in plasma are measured by standard methods well known to those skilled in the art. (See, for example, R. Neri and M. Monahan, Invest. Urology (1972), 10, 123-130 for prostatic P staining and E. Nieschlay and D. L. Loriaux, Z. Klin Chem. Klin Biochem (1972), 4, 164 for radioimmunoassay determinations of T.)

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The prostate volume is measured by rectal examination and/or by transrectal ultrasonography. Objective assessment of the effect of treatment is also measured by physical methods well known to these skilled in the art of nuclear magnetic resonance imaging, as well as by physical examination.

Using a protocol similar to that described above, clinical trials on the effect of the combination of finasteride and fadrazole will exhibit an even greater effect on alleviating the symptoms of BPH in patients which will be greater than either agent alone.

The method of preparing the compounds of the present invention, already described above in general terms, may be further illustrated by the following examples which should not be construed as being limitations on the scope or spirit of the instant invention.

#### CHAPTER 1

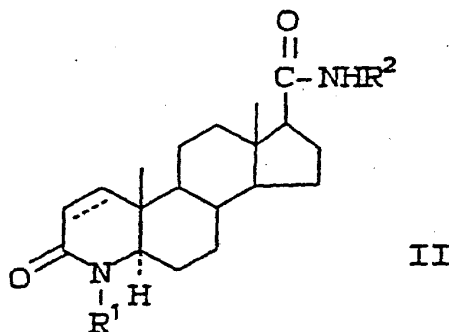
##### EXAMPLE 1

##### Methyl 3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxylate

A suspension of 83.7 g of methyl 3-oxo-4-aza-5 $\alpha$ -androstane-17-carboxylate\* and 126.5 g of benzeneseleninic anhydride in 2.09 l of chlorobenzene was heated at reflux for 2 hours. The reflux condenser was switched to a distillation head and the mixture was distilled slowly to remove water that had formed in the reaction (2 hours). The solution was evaporated to leave 198 g of wet residue. The resi-

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due as a solution in dichloromethane was washed with saturated aqueous  $\text{NaHCO}_3$  solution and saturated  $\text{NaCl}$  solution, then dried and evaporated to leave 172.4 g. This material was chromatographed on 2.56 kg of silica gel eluting first with dichloromethane (5 l) and then with 4:1 dichloromethane acetone. The desired product eluted after 8 l and amounted to 53.4 g. It was rinsed with diethyl ether and dried to leave 49.5 g, of the title compound m.p.  $278-280^\circ\text{C}$ . In a similar fashion the following compounds were converted to their corresponding 1,2-unsaturated derivatives:



		m.p.
1a	$\text{R} = \text{CONHC}(\text{CH}_3)_3$	$252-254^\circ\text{C}$
1b	$= \text{CONHC}(\text{CH}_3)_2\text{CH}_2\text{C}(\text{CH}_3)_3$	$224-226^\circ$

\* Rasmusson Johnston and Arth.

U.S. Patent 4,377,584, March 22, 1983.



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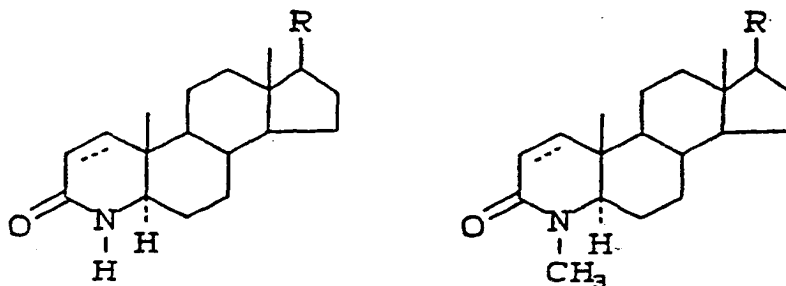
EXAMPLE 2Methyl 4-methyl-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxylate

5 A suspension of 25 g of the product of Example 1 and 2.25 g of sodium hydride in 500 ml of dry dimethylformamide was stirred under nitrogen for 15 minutes. Methyl iodide (15 ml) was added dropwise and the mixture was stirred for 30 minutes at room temperature. Additional (5 ml) methyl iodide  
 10 was added and the mixture was heated at 50°C for 2 hours. After cooling the mixture was diluted with water to a volume of 2 liters. The solid was separated after cooling and amounted to 25.4 g, m.p. 159-161°C.

15 In a similar fashion the following compounds were converted to their corresponding 4-methyl derivatives:

20

25



30

2a R = CONHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>,  
androstane

m.p.  
148-150°C

2b = CONHC(CH<sub>3</sub>)<sub>3</sub>;  $\Delta$ -1-androstene 153-155°

2c = CONHC(CH<sub>3</sub>)<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)<sub>3</sub>  $\Delta$ -1-androstene 168-170°

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EXAMPLE 3

S-(2-Pyridyl) 4-methyl-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate

5 A suspension of 25 g of the product of Example 2 in 125 ml of methanol was treated with a solution of KOH (\*12.5 g) in 12.5 ml of water. After refluxing for 4 hours, the solution was acidified with 6 NHCl and then was diluted with water. The crude acid (23.32 g) was separated, dried and had  
10 m.p. 300°C.

The crude, dry acid (23 g), triphenylphosphine (36.45 g) and 2,2'-dipyridyldisulfide (30.4 g) were suspended in 138 ml of toluene with stirring for 3 hours at room temperature. The  
15 reaction mixture was directly chromatographed on a column of 4.5 kg of silica gel eluting with 9:1 ethyl acetate-acetone to give 20.4 g of the desired product, m.p. 218-220°C.

Continued elution with acetone gave 5.2  
20 g of the methanol addition product, S-(2-pyridyl) 1 $\alpha$ -methoxy-4-methyl-3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -thiocarboxylate, m.p. 221-223°C as a by-product.

3A. In a similar fashion the product of Example 1 was converted into S-(2-pyridyl)  
25 3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate, m.p. 230-232°C.

3B. In a similar manner methyl 3-oxo-4-aza-5 $\alpha$ -androstane 17-carboxylate was converted into  
30 S-(2-pyridyl) 3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -thiocarboxylate, m.p. 232-234°C.

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EXAMPLE 4N-t-butyl 4-methyl-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide

5           Anhydrous t-butylamine was added to a suspen-  
sion of 2.5 g of the pyridylthioester of Example 3 in  
70 ml of tetrahydrofuran. After 60 minutes exposure,  
the resulting solution was evaporated and the residue  
was chromatographed on 125 g of silica gel. Elution  
with 20:1 ethyl acetate dichloromethane afforded 1.5 g  
10 of the product, m.p. 152-154°C.

When the example is repeated using an appro-  
priate amine and an appropriate pyridylthioester, the  
following products were obtained:

15       4b: N-t-butyl 3-oxo-4-aza-5 $\alpha$ -androstande-17 $\beta$ -  
carboxamide, m.p. 275-276°C.

4c: N-(2,4,4-trimethyl-2-pentyl) 4-methyl-3-oxo-4-  
aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -carboxamide, m.p. 168-  
170°C.

20

EXAMPLE 55-Oxo-3.5-secoetian-3.20-dioic acid

To a solution of 200 g of 3-oxo-4-etien-  
17 $\beta$ -oic acid in 3.5 l of t-butanol at 80° was added a  
solution of 198.4 g of sodium carbonate in 474 ml of  
25 water. A warm (65°C) solution of 948.5 g of sodium  
metaperiodate and 6.95 g of permanganate in 3.5 l  
of water was added at such a rate that the reaction  
mixture was maintained at 80°C. After addition the  
mixture was heated at reflux for one hour. The  
30 mixture stood at room temperature overnight. The  
inorganic salts were removed by filtration and the  
cake was washed with 225 ml of water. A solution of

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5% aqueous sodium bisulfite was added to reduce the iodine that was present. The *t*-butanol was removed under reduced pressure and the aqueous residue was acidified with conc. hydrochloric acid. The separated  
5 gum was extracted into dichloromethane and was washed with 5% aqueous sodium bisulfite, saturated sodium chloride solution, then dried and concentrated to an off-white residue (214 g). Crystalline material was obtained by suspending the residue in ether and  
10 diluting with hexane to give 152 g, m.p. 189-192°C.

EXAMPLE 5B3-Oxo-4-aza-5-etien-20-oic acid

A suspension of 64.7 g of the dioic acid of  
15 Step 5 in 350 ml of ethylene glycol was treated with 80 ml of liquid ammonia. The resulting solution was heated at a rate of 3°/min. up to 180°C and was held at that temperature for 15 minutes. After cooling,  
1 liter of water was added and the mixture was  
20 acidified with 10% hydrochloric acid to a pH of 1.5. The product was removed and washed with water, then air dried to leave 57.5 g of the product, m.p. 310°C.

EXAMPLE 5C3-Oxo-4-aza-5 $\alpha$ -etian-20-oic acid

A solution of 136 g of the 5-acid of Example  
25 5B in 16.32 ml of acetic acid was hydrogenated at 60°C in the presence of platinum catalyst (from 16.32 g of PtO<sub>2</sub>) at 40 psig for 3 hours. The catalyst was  
30 removed and the solution concentrated to give 128.2 g of crude product. The material was washed well with 3 l of water then filtered and air dried to leave 125 g of the white solid, m.p. 310°.

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5 This material is also obtained by saponification of methyl 3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxylate (methyl 3-oxo-4-aza-5 $\alpha$ -etien-17 $\beta$ -oate) in 7% methanolic potassium hydroxide followed by an acidic work-up.

#### EXAMPLE 5D

N-(2,4,4-trimethyl-2-pentyl)3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide

10 A solution of 5.0 g of the product of Example 5C, 3.35 g of dicyclohexylcarbodiimide and 3.18 g of 1-hydroxybenztriazole in 500 ml of dichloromethane was stirred at room temperature overnight. The solid was separated by filtration  
15 and the filtrate was treated with 2,4,4-trimethyl-2-pentylamine (t-octylamine). This solution stood at room temperature for 64 hours. A small amount of solid was removed and the solution was washed successively with 10% aqueous sodium hydroxide,  
20 water, 10% hydrochloric acid and saturated aqueous sodium chloride. After drying and concentration the crude product was eluted through 240 g of silica gel with 3:7 acetone-dichloromethane to give 5.5 g of the product, m.p. 250-251°C.

25

#### EXAMPLE 5E

Example 5D is repeated using t-butylamine in place of 2,2,4-trimethyl-2-pentylamine to obtain N-t-butyl 3-oxo-4-aza-5 $\alpha$ -androstane-17 $\beta$ -carboxamide,  
30 m.p. 274-276°C.

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EXAMPLE 6Synthesis of 17B(N-1-adamantyl-carbamoyl)-  
4-aza-5 $\alpha$ -androst-1-en-3-one

5                   100 mg of the 17-methyl ester (0.305 mmoles)  
from Example 1 was suspended in 3.0 ml of THF (dried  
over molecular sieves 3A), and then was added 183.0 mg  
of 1-adamantanamine (1.2 mmoles). The suspension was  
cooled to 5-10°C and then 590  $\mu$ l of 2.0 M solution,  
10 of EtMgBr in THF was added. The resulting mixture was  
allowed to stir for 10 minutes, and then refluxed for  
1-2 hours under N<sub>2</sub>. The mixture was cooled to 0°C  
and then quenched with saturated solution of NH<sub>4</sub>Cl  
15 (about 10 ml.). The organic layer was separated and  
the aqueous layer extracted with three volumes CH<sub>2</sub>Cl<sub>2</sub>.

The organic layers were combined, washed 2  
times with H<sub>2</sub>O, twice with saturated sodium chloride,  
and dried over MgSO<sub>4</sub>, filtered and evaporated to  
dryness in vacuum. Crystallization from EtOAc  
20 afforded 75.0 mg of product. Recrystallization from  
MeOH and drying at 110°C for 2 hours/0.1 mm gave  
product, mpt. 305-306°C. Molecular weight (by FAB)  
showed M<sup>+</sup>=451: Calculated =451.

Anal. Calcd. for C<sub>29</sub>H<sub>42</sub>N<sub>2</sub>O<sub>2</sub>:  
25                   C, 77.28; H, 9.40; N, 6.21.  
Found: C, 76.84; H, 9.73; N, 5.93.

30

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EXAMPLE 7Synthesis of 17 $\beta$ -(N-2-adamantyl-carbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one

- 5           Following the above-described general  
procedure of Example 6 but utilizing 2-adamantamine  
(prepared by aqueous neutralization of the hydro-  
chloride and EtOAc extraction and isolation) in place  
10 of 1-adamantamine, and carrying out the reflux for 7  
hours rather than 1-2 hours, the title compound is  
prepared, mpt. 284-285°C.

EXAMPLE 8

- 15           Synthesis of 17 $\beta$ -(N-1-adamantylcarbamoyl)-4-aza-5 $\alpha$ -  
androstane-3-one

- 100.0 mg of the adamantyl derivative  
produced in Example 6 was dissolved in 5.0 ml of dry  
THF. 300 mg of 5% Pd/C was added and the mixture  
20 was hydrogenated for 6.0 hrs. at R.T. at 40 psi.  
The mixture was filtered through celite, the cake  
washed with THF (3 times) and solvent evaporated  
under vacuum to yield 97.0 mg. of crude above-titled  
product. NMR showed absence of olefins. The crude  
25 material was placed on 15.0 g silica gel column, and  
eluated with 1:1(CH<sub>2</sub>Cl<sub>2</sub>: acetone).

- Collected fractions afforded a single  
spot material by TLC weighing 77.98 mg. NMR was  
in excellent agreement with the proposed structure.  
30

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Recrystallized from EtOAc to yield 65.59 mg of the above-titled product, mp. 323-324°C.

Anal. Calcd. for  $C_{29}H_{44}O_2N_2 \cdot 1/4 H_2O$ :

C, 76.18; H, 9.81; N, 6.13.

5 Found: C, 75.91; H, 9.97; N, 6.06.

#### EXAMPLE 9

#### 10 Synthesis of 17B(N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 $\alpha$ -androst-1-en-3-one

120 mg of the thiopyridyl ester of Example 3 was suspended in 20 ml of dry THF, to the suspension was added 175.0 mg of 1-adamantanamine under  $N_2$ . The reaction was carried out at R.T. for 16 hours under  
15  $N_2$ . The reaction was monitored by silica gel TLC, using 1:1 acetone: hexane. The product was separated on TLC 20 cm x 20 cm, 1000  $\mu$ m silica gel plate, eluted with 1:1 (acetone/hexane).

The product was crystallized from ethyl acetate, to  
20 give 50.0 mg of pure material m. pt. 202-205°C.

Molecular Weight (FAB) showed 465; Calc: 465.

Recrystallization afforded 19.14 mg of the above-titled product, m.pt. 202-202.5°C.

Anal. Calcd for  $C_{30}H_{44}N_2O_2 \cdot H_2O$ :

25 C, 74.64; H, 9.60; N, 5.80.

Found: C, 74.32; H, 9.47; N, 5.89.

30



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EXAMPLE 10Hydrolysis of Methyl-3-oxo-4-aza-5 $\alpha$ -androstande-17 $\beta$ -carboxylate

5           The 17 $\beta$ -androstande carboxylate starting material of Example 1 was hydrolyzed with 7% KOH in isopropanol or aqueous methanol, followed by an acidic work-up to give the corresponding 17 $\beta$  carboxylic acid which was utilized in Example 11.

EXAMPLE 11N-(1-adamantyl)-3-oxo-4-aza-5 $\alpha$ -androstande-17 $\beta$ -carboxamide

15           A solution of 5.0 g of the product of Example 10, 3.35 g of dicyclohexylcarbodiimide and 3.18 g of 1-hydroxybenztriazole in 500 ml of dichloromethane was stirred at room temperature overnight. The solid was separated by filtration and the filtrate was  
20           treated with 1-adamantamine. This solution stood at room temperature for 64 hours, then filtered, and the solution was washed successively with 10% hydrochloric acid and saturated aqueous sodium chloride. After  
25           drying with MgSO<sub>4</sub>, it was filtered and concentrated. The crude product was eluted through 240 g of silica gel with 3:7 (acetone-dichloromethane) to give 5.5 g of the above-titled product, m.p. 323-324°C.

30

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EXAMPLE 12Synthesis of Benzotriazol-1-yl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstan-17 $\beta$ -carboxylate

5           A suspension of 83.7 g of methyl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstan-17 $\beta$ -carboxylate. (See Rasmusson, et al. J. Med. Chem. 29, 2298-2315, 1986) was hydrolyzed with 7% KOH in aqueous methanol, followed by an acidic work up to give the corresponding

10       17 $\beta$ -carboxylic acid.

          The acid was readily converted into benzotriazol-1-yl-3-oxo-4-methyl-4-aza-5 $\alpha$ -androstan-17 $\beta$ -carboxylate as described in Example 13. The activated ester (the benzotriazol derivative) was

15       purified on TLC (4 plates, 20 cm x 20 cm x 20 cm x 1000 $\mu$ m silica gel) eluted with 4:96 (MeOH-CHCl<sub>3</sub>). The isolated product was washed with ether to give the active ester m.pt. 198-200°C with decomposition.

EXAMPLE 13Synthesis of 17 $\beta$  (N-1-adamantylcarbamoyl)-4-methyl-4-aza-5 $\alpha$ -androstan-3-one

25       100.0 mg of the 4-methyl-4-aza-benzotriazole derivative prepared as described in Example 12, was dissolved in 20.0 ml CH<sub>2</sub>Cl<sub>2</sub>. To the clear solution was added 127 mg of 1-adamantamine. The reaction mixture was stirred overnight at R.T./N<sub>2</sub>.

30       Crystallization from EtOAc after filtering the solution through Teflon Acrodisc CR afforded 26.32 mg, m.pt. 210-217°C. The product was further purified on 1.0 g silica gel column (EM silica gel)

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with 1:1 (acetone-hexane) as eluant to give after recrystallization (ethyl acetate) 21.75 mg of white needles of the above-titled product, m.pt. 203-205°C.

Anal. Calcd. for  $C_{30}H_{46}N_2O_2 \cdot 1.5 H_2O$ :

5 C, 73.58; H, 9.68; N, 5.62;

Found: C, 73.15; H, 9.30; N, 5.67.

#### EXAMPLE 14

10 Diastereomeric Synthesis of 17B(N-exo-2-norbornanyl-carbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one)

100.0 mg of the corresponding 4-H thiopyridyl ester of Example 3, prepared by the procedure of Example 3, but utilizing the 4-H methyl ester product of Example 1, (See Rasmusson *et al.* J. Med. Chem. Vol. 29, pp. 2298-2315 (1986), was dissolved in 3.0 ml of dry THF under  $N_2$ . To the clear solution was added 477  $\mu$ l of ( $\pm$ ) racemic exo-2-aminonorbornane. Allowed the reaction to proceed for 16 hours at R.T./ $N_2$ . The reaction mixture was evaporated to dryness in vacuum. The residue was dissolved in chloroform. The organic layer was washed with 2.5 N HCl acid (3 times); 3 times with water; 3 times with saturated NaCl solution, dried over  $MgSO_4$ , filtered and evaporated to dryness in vacuum to afford 56.3 mg of a racemic diastereomeric mixture.

The crude product was chromatographed on TLC (2 plates, 20 cm x 20 cm x 500  $\mu$ m silica gel) eluted with 70:30 ( $CHCl_3$ :acetone) to yield 43.4 mg. of the above-titled product. Recrystallization from EtOAc yielded 30 mg product, m.pt 245-245.9°C.

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NMR (CDCl<sub>3</sub>) confirmed the above structure.

FAB mass spectrum calcd. for C<sub>26</sub>H<sub>38</sub>O<sub>2</sub>N<sub>2</sub>: m/e  
411; Found: 411.

5      Anal. Calcd. for C<sub>26</sub>H<sub>38</sub>O<sub>2</sub>N<sub>2</sub>.H<sub>2</sub>O:  
          C, 72.82; H, 9.40; N, 6.58.  
Found: C, 73.21; H, 9.20; N, 6.25.

#### EXAMPLE 15

10

Synthesis of 17β(N-1-adamantylmethylcarbamoyl)-  
4-aza-5α-androst-1-en-3-one

15      200.0 mg of the 4-H thiopyridyl aza steroid,  
used in Example 14, was suspended in 2.0 ml of dry  
THF.

20      To the suspension was added 400 μl of 1-  
aminomethylene adamantane via syringe at R.T./N<sub>2</sub>.  
After several minutes, a yellow clear solution  
resulted and after 1/2 hr., precipitation occurred.  
The reaction was allowed to proceed overnight/N<sub>2</sub>.  
Diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed with 10% NaOH, two times,  
then with H<sub>2</sub>O two times, followed by 10% HCl (two  
times), H<sub>2</sub>O (two times), and finally two times with  
25      satd. NaCl solution.

30      The organic layer was dried over MgSO<sub>4</sub>,  
filtered, concentrated in vacuo to obtain the  
product, as shown by NMR, recrystallized from EtOAc,  
to yield 149.0 mg product, m.pt 255-257°C with  
decomposition.

FAB Mass Spectrum, Calcd: m/e 464 + 1 = 465:  
Found 465.

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EXAMPLE 16Synthesis of 17B-(N-2-adamantylcarbamoyl)-  
4-aza-5 $\alpha$ -androstan-3-one

- 5           A mixture of 1.09 grams 17B-(N-2-adamantyl-  
carbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one (See Example  
10 for preparation), 150 ml of ethanol, and 1.0 g. of  
30%  
Pd/C was hydrogenated overnight with shaking under 45  
10   psig. hydrogen pressure. The suspension was filtered  
to remove catalyst, and evaporated to dryness to yield  
a grey residue. This was chromatographed by elution  
on a 200 ml silica gel column with 40:60 acetone/  
methylene chloride eluant to yield 1.0 g of solid,  
15   mp. 294-296°C.  
Anal. Calcd. for  $C_{29}H_{44}N_2O_2 \cdot 0.2H_2O$   
Calcd. C, 76.33; H, 9.80; N, 6.14  
Found C, 76.23; H, 9.86; N, 5.92  
Mass Spec. Analysis by electron impact showed  
20   MW of 452.

EXAMPLE 17Synthesis of 17B-(N-2-adamantylcarbamoyl)-  
4-aza-4-methyl-5 $\alpha$ -androst-1-en-3-one

- 25           A suspension of 500 mg of 17B-(N-2-adamantyl-  
carbamoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one, as prepared  
in Example 16, 10 ml sieve-dried DMF, 140 mg NaH, were  
heated and stirred at 70°C under a nitrogen atmosphere  
30   for 18 hours. Cooled to room temperature and then  
added 0.4 ml methyl iodide dropwise with stirring  
which was continued at 50°C for 3 hours. The reaction  
mixture was then treated by cooling to room

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temperature, followed by the addition of 15 ml water. The mixture was extracted with 3 x 20 ml of CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were combined, washed with brine, dried and evaporated to yield a white crystalline residue. Recrystallization from ethyl acetate/CH<sub>2</sub>Cl<sub>2</sub> yielded a pure white solid, mp 246-248°C.

Analysis calculated for C<sub>30</sub>H<sub>44</sub>N<sub>2</sub>O<sub>2</sub>•0.3H<sub>2</sub>O

Calcd. C, 76.65; H, 9.56; N, 5.95

Found C, 76.50; H, 9.75; N, 5.84

Mass spectroscopy showed a molecular weight of 464.

#### EXAMPLE 18

Synthesis of 17B-(N-2-adamantylcarbamoyl)-  
3-oxo-4-methyl-4-aza-5α-androstane

17B-(N-2-adamantylcarbamoyl)-4-methyl-4-aza-androsten-1-en-3-one, (200 mg) as prepared in Example 17, were placed into 25 ml absolute ethanol with 200 mg 30% Pd/C hydrogenation catalyst. The suspension was rocked overnight under 40 psig hydrogen pressure.

The suspension was filtered, and the filtrate evaporated to dryness. The residue was recrystallized from hot ethyl acetate to give a white crystalline solid, mp. 113-115°C. Calcd. for C<sub>32</sub>H<sub>50</sub>N<sub>2</sub>O<sub>3</sub>•0.5 EtOAc

Calcd: C, 75.25, H, 9.86, N, 5.48

Found C, 75.07; H, 9.52; N, 5.28

Mass spectroscopy depicted a molecular weight of 466 for the non-solvated molecule.

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EXAMPLE 19

Synthesis of 17B-(N-methyl-N-2-adamantyl)  
carbamoyl-4-methyl-4-aza-androst-1-en-3-one

5           17B-(N-2-adamantyl)carbamoyl-4-aza-androst-1-en-3-one (5.0 g) and 1.5 g sodium hydride in 100 ml dry DMF were stirred under dry nitrogen for 3 hours at 40°C. The reaction was cooled to room temperature and about 4 ml of methyl iodide was added dropwise  
10 and allowed to stir at room temperature for one hour. The reaction was cooled in an ice bath and a large excess of about 250 ml, water was added. The aqueous mixture was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 100 ml), the organic extracts combined, washed with H<sub>2</sub>O,  
15 brine, and then evaporated to dryness to yield crude product. The crude product was eluted on an HPLC column (Si gel) with 10/1 acetone/CH<sub>2</sub>Cl<sub>2</sub> to yield 2 peaks having retention times of 3 CV(B) and 3.8 CV(A). Peak (A) was analyzed as per the 4-methylaza titled  
20 product of Example 15. The second product (B) was analyzed as the 4-methylaza-17B-(N-methyl-N-2-adamantyl)carbamoyl analog, i.e. the titled compound, mp. 163-165.

Calcd. for C<sub>31</sub>H<sub>46</sub>N<sub>2</sub>O<sub>2</sub>

25   Calcd. C, 77.77; H, 9.68; N, 5.85

Found C, 77.29; H, 9.79; N, 5.77

Mass spectrometry showed a molecular weight of 478.

30

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EXAMPLE 20

Synthesis of 17B-(N-methyl-N-2-adamantylcarbamoyl)  
4-aza-4-methyl-androstan-3-one

- 5           The crude reaction mixture from Example 19  
(4.6 g) was dissolved in 200 ml ethanol and together  
with 1.0 g 30% Pd/C was hydrogenated under 40-45 Psig  
a hydrogen atmosphere at room temperature overnight.  
The mixture was filtered, residue washed with ethanol.  
10   The ethanol solution was evaporated to dryness to  
yield a crude mixture. Recrystallized from CH<sub>2</sub>Cl<sub>2</sub>/  
diethyl ether/hexane to yield 800 mg of the pure  
monomethyl androstane compound of Example 16, mp  
113-115°C. Second and third crops were combined with  
15   mother liquor and treated by HPLC as in Example 17 to  
yield the dimethylated title compound, mp 180-182°C.  
Anal. Calcd. for C<sub>31</sub>H<sub>48</sub>N<sub>2</sub>O<sub>2</sub>  
Calcd. C, 77.45; H, 10.06; N, 5.83  
Found C, 77.26; H, 9.87; N, 5.82  
20   Mass spectrometry showed a molecular weight of 480.

EXAMPLE 21

25   N-t-Butyl Androst-3,5-diene-17B-carboxamide-3-Car-  
boxylic Acid

(a) N-t-butyl androst-3,5-diene-3-bromo-17B-  
carboxamide

- 30           To a solution of oxalic acid (0.0011 mol,  
0.1 g) and oxalyl bromide (0.0211 mol, 3 ml) in 15 ml  
of sieve dried toluene was added over a one hour  
period 1 g (0.003 mol) of androst-4-ene-3-one



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17 $\beta$ -carboxylic acid. The reaction was stirred at room temperature for 2 hours and then it was concentrated in vacuo. The excess oxalyl bromide was removed by azetoroping with toluene. The resulting  
5 brown oil was redissolved in toluene, cooled to 0°C and then 10 ml t-butylamine (7.0 g) in 30 ml of toluene was added dropwise over 15 minutes. Once the addition was complete, the reaction was stirred at 0°C for 15 minutes and then it was kept at -20°C for  
10 19 hours. The reaction mixture was allowed to warm to room temperature and then stirred at 25°C for one hour. The volatiles were removed in vacuo. The residue was partitioned between chloroform/water, the layers were shaken together and separated and then  
15 the aqueous phase was back-extracted twice with chloroform. The combined organic extracts were washed with water (2x) and then dried with anhydrous magnesium sulfate. The crude product was purified by flash chromatography on silica; eluting with 20%  
20 ethyl acetate in hexane, to give 1.06 g of the title compound, a white solid.

(b) N-t-Butyl Androst-3,5-diene-17 $\beta$ -carboxamide-3-carboxylic acid

25 To a solution of N-t-Butyl Androst-3,5-diene-3-bromo-17 $\beta$ -carboxamide (0.5 g, 0.00115 mol) in 5 ml of tetrahydrofuran, cooled to -78°C (dry ice/acetone bath) under argon, was added dropwise 1.5 ml (0.00375 mol) of a 2.5 M solution of n-butyl  
30 lithium in hexane. The reaction mixture was stirred at this temperature for one hour and then carbon dioxide was bubbled into the reaction for 45 minutes,

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via a concentrated sulfuric acid tower. The reaction mixture was allowed to warm to room temperature and then it was diluted with water, aqueous HCl solution and chloroform. The layers were shaken together and separated, with the aqueous phase being back-extracted with chloroform (2x). The combined organic extracts were washed with water (2X), and brine (1 x) and then dried with anhydrous magnesium sulfate. The solvents were removed under reduced pressure give 0.6 g of a crude solid. This material was slurried with hexane and a white solid was isolated (0.43 g). The title compound was recrystallized from acetonitrile, m.p. 247°-250°.

## CHAPTER 2

## EXAMPLE 1

Methyl 3-oxo-4-aza-5a-androst-1-ene-17B-carboxylate

A suspension of 83.7 g of methyl 3-oxo-aza-5a-androstane-17-carboxylate\* and 126.5 g of benzeneseleninic anhydride in 2.09 l of chlorobenzene was heated at reflux for 2 hours. The reflux condenser was switched to a distillation head and the mixture was distilled slowly to remove water that had formed in the reaction (2 hours). The solution was evaporated to leave 198 g of wet residue. The residue as a solution in dichloromethane was washed with saturated aqueous NaHCO<sub>3</sub> solution and saturated NaCl solution, then dried and evaporated to leave 172.4 g. This material was chromatographed on 2.56 kg of silica gel eluting first with dichloromethane (5 liters) and then with 4:1 dichloromethane-acetone. The desired product was eluted with 8 liters of the

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above-mixed solvent and evaporated to dryness in vacuo to yield 53.4 g solid. It was washed with diethyl ether and dried to leave 49.5 g of the above-titled product, m.p. 278-280°C.

5

\*Rasmusson Johnston and Arth. U.S. Patent 4,377,584, March 22, 1983.

#### EXAMPLE 2

10

S-(2-Pyridyl)-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thio-carboxylate

15

A suspension of 25.0 g of the above product from Example 1 was saponified with 12.5 g of KOH in 150.0 ml of 5:1 CH<sub>3</sub>OH-H<sub>2</sub>O under reflux conditions for 4 hours/N<sub>2</sub>. The mixture was cooled to 25°C and acidified to pH <2. Water (175 ml) was added gradually with stirring to leave a crystalline precipitate which was collected and washed with water.

20

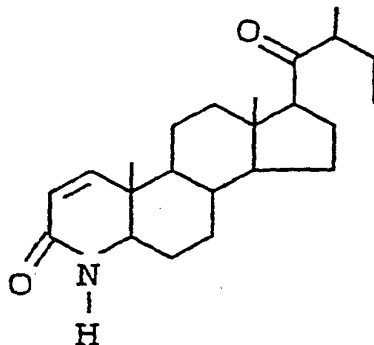
After drying, the product amounted to 25 g., m.pt 313-315°C with decomposition.

25

The crude dry acid (23.0 g) was suspended in 210 ml of toluene, and to the suspension was added triphenylphosphine (56.0 g) and 2,2'-dipyridyl disulfide (48.3g), and the mixture was stirred at 24°C overnight/N<sub>2</sub>. The reaction mixture was placed on a column of silica gel (1.3 kg) and was eluted with 1:1 (acetone/CH<sub>2</sub>Cl<sub>2</sub>). The desired thioester eluted slowly, and after rinsing with ether, yielded 36.8 g of the above-titled product, m.p. 232-235°C.

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EXAMPLE 322-Methyl-4-aza-21-nor-5 $\alpha$ -chol-1-ene-3,20-dione

To a solution of 7.2 g of S-(2-pyridyl)-3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate in 288 ml of tetrahydrofuran was added at -78°C 33.6 ml of 1.3M S-butylmagnesium chloride. After 30 minutes at -78°C the solution came to room temperature and was treated with saturated aqueous NaCl solution. The product was extracted into dichloromethane and was washed with saturated aqueous NaCl solution and 10% aqueous NaOH solution, then dried and concentrated. The residue was eluted through 430 g of silica gel with 9:1 dichloromethane-acetone to give 4.5 g of the product, m.p. 246-249°C.

When the procedure is repeated using the following reagents, the indicated product is obtained.

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	<u>Starting Material</u>	<u>Reagent</u>	<u>Product</u>
5	S-(2-pyridyl)3-oxo-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate	2-pyrrolyl magnesium chloride	17 $\beta$ -(2-pyrrolyl-carbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one m.p. 294-296°C
10	S-(2-pyridyl)3-oxo-4-methyl-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate	sec-butyl magnesium chloride	4,22-dimethyl-4-aza-21-nor-5 $\alpha$ -chol-1-ene-3,20-dione m.p. 134-136°C
15 20	S-(2-pyridyl)3-oxo-4-methyl-4-aza-5 $\alpha$ -androst-1-ene-17 $\beta$ -thiocarboxylate	2-pyrrolyl magnesium chloride	4-methyl-17 $\beta$ -(2-pyrrolylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one m.p. 234-238°C
25	S-(2-pyridyl)3-oxo-4-aza-5 $\alpha$ -androst-ene-17 $\beta$ -thiocarboxylate	isobutyl magnesium chloride	23-methyl-4-aza-21-nor-5 $\alpha$ -cholane-3,20-dione m.p. 220-222°C

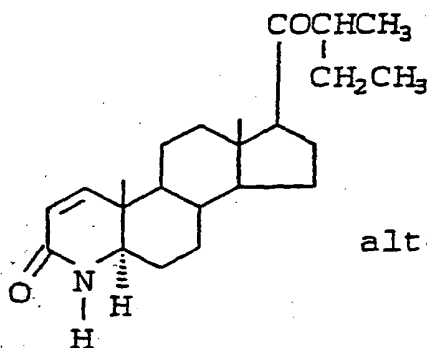
30

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EXAMPLE 422-Methyl-4-aza-21-nor-5 $\alpha$ -chol-1-ene-3,20-dione

5

10



alternate route

15

20

25

A solution of 21 g of 22-methyl-4-aza-21-nor-5 $\alpha$ -cholane-3,20-dione and 29.49 g of benzeneseleninic anhydride in 552 ml of chlorobenzene was refluxed with water separation for 4 hours. The mixture was concentrated and the residue was redissolved in dichloromethane. After washing with 10% aqueous sodium hydroxide, then 10% hydrochloric acid and saturated aqueous sodium chloride the solution was dried and concentrated to 45 g of yellow residue. This was chromatographed on 1.5 kg of silica gel packed in dichloromethane and eluted with ethyl acetate to give 10.6 g of the product, m.p. 248-251°C.

30

When the procedure is repeated using 23-methyl-4-aza-21-nor-5 $\alpha$ -cholane-3,20-dione as starting material the product obtained is 23-methyl-4-aza-21-nor-5 $\alpha$ -chol-1-ene-3,20-dione, m.p. 283-286°C.

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EXAMPLE 517 $\beta$ -(phenylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one

To a stirred suspension of 43 g of  
5 S-(2-pyridyl)-3-oxo-4-aza-5- $\alpha$ -androst-1-ene-17-  
beta-thiocarboxylate in 500 ml of anhydrous tetra-  
hydrofuran (THF) was added at -78°C a THF solution of  
157 ml of 2N phenylmagnesium chloride over 60  
minutes. After stirring at -78°C for 60 minutes, the  
mixture was brought to -30°C and was quenched by  
10 addition of 10% HCl while maintaining the temperature  
below -20°C. After warming to 0°C, the mixture was  
diluted with 2000 ml of water and extracted with 4000  
ml of dichloromethane in portions. The organic layer  
was washed sequentially with water, 1N sodium  
15 hydroxide, water and saturated sodium chloride  
solution. Drying with MgSO<sub>4</sub> and concentration  
afforded 37.5 g of crude product. Recrystallization  
from dichloromethane/ ethyl acetate gave the title  
phenyl ketone (30.4 g, 77% yield).  
20 m.p. 290-291°C.

	Calc	Found
N	3.61	3.56
C	77.48	77.16
H	8.26	8.19

25

EXAMPLE 617-beta-4-fluorophenylcarbonyl-4-aza-5- $\alpha$ -androst-1-ene-3-one

The procedure of Example 5 was repeated  
30 except using p-fluorophenylmagnesium bromide as the  
Grignard reagent and the title compound was  
obtained. m.p. 315-315.5°C.

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EXAMPLE 717B-(cyclohexylcarbonyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one

To a suspension of 34.8 g of the thiopyridyl ester of Example 2 in 700 ml of anhydrous THF was added at -65 degrees C 130 ml of a 2 M ether solution of cyclohexyl magnesium chloride over a period of 20 minutes. After stirring at -70 degrees C for 60 minutes the solution was warmed and stirred at -10 degrees C for 60 minutes. The mixture was diluted with 500 ml of dichloromethane and then dropwise with dichloromethane, the phases were separated and the organic layer was treated sequentially with water, 1 N sodium hydroxide, water and saturated sodium chloride solution. The organic solution was decolorized with charcoal, filtered and concentrated to a residue which was crystallized from ethyl acetate to give 28.2 of the title compound, m.p. 271.5-277 degrees C.

EXAMPLE 8

The title compound of Example 7 was also prepared by the following procedure.

To a mixture of 150 g of methyl 3-oxo-4-aza-5-alpha-androst-1-ene-17-beta-carboxylate in 2800 ml of anhydrous THF was added with stirring at less than 0 degrees C internal temperature 678 ml of a 2 N ether solution of cyclohexyl magnesium chloride. The solution was then refluxed for 6 hours. The cooled (less than 10 degrees C) reaction mixture was acidified with 10% HCl solution and was extracted with dichloromethane. The organic layer



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was washed sequentially with water, saturated NaHCO<sub>3</sub> solution and saturated NaCl solution. Drying (MgSO<sub>4</sub>) and evaporation left 163 g of crude cyclohexyl ketone. Recrystallization from dichloromethane/ethylacetate gave 131 g of the pure material.  
m.p. 269-270 degrees C.

	% Calc.	Found
N	3.61	3.61
C	77.37	77.37
H	9.74	10.13

EXAMPLE 9

17-beta-(cyclopentylcarbonyl)-4-aza-5-alpha-androst-1-ene-3-one

When the procedure of Example 7 or 8 was repeated using cyclopentylmagnesium chloride, the title compound was obtained:

m.p. 272-273 degrees C.

	Calc	Found
N	3.66	3.78
C	75.25	74.89
H	9.60	9.54

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EXAMPLE 10

17-beta-(cyclobutylcarbonyl)-4-aza-5-alpha-androst-1-ene-3-one

5 When the procedure of Example 7 or 8 was repeated using cyclobutylmagnesium chloride, the title compound was obtained:

m.p. 288-289 degrees C.

10		%Calc	Found
	N	3.94	3.87
	C	77.71	78.06
	H	9.36	9.61

15 EXAMPLE 11

Synthesis of 17-B-(4-Phenylbenzoyl)-4-aza-5a-androst-1-en-3-one

20 To a suspension of 258.0 mg of dry activated magnesium chips in 5.0 ml of dry THF was added 932.0 mg of 4-bromobiphenyl in 5.0 ml of dry THF under N<sub>2</sub>. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 30 ml of 1,2-dibromoethane/N<sub>2</sub>. The reaction was allowed to proceed for 1-1 1/2 hours at 28°C/N<sub>2</sub>. The concentration of the Grignard reagent was 4.0 mmoles in 10.0 ml of dry THF.

25 The steroid from Example 2 (205.0 mg, 0.5mmol of thiopyridyl ester) was suspended in 2.0 ml of dry THF, cooled to -80°C and the above Grignard 3.80 ml was added via syringe to the steroidal

30

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suspension over 5-10 minutes/ $N_2$ . The reaction was allowed to proceed for 1 hour at  $-80^\circ C/N_2$  and then at  $-10^\circ C$  for an additional hour/ $N_2$ . The solution was diluted with 10.0 ml of methylene chloride and quenched with saturated aqueous solution of  $NH_4Cl$  to pH=4. The organic layers were separated, washed 3 times with water, 3 times with saturated sodium chloride, dried over  $MgSO_4$ , filtered, and evaporated under vacuum to afford 156.2 mg of crude product. Crystallization from EtOAc gave the above-titled product in 98.58 mg, m.pt.  $290^\circ C-290.5^\circ C$ .

Anal. Calcd. for  $C_{31}H_{35}NO_2$ :

C, 82.08; H, 7.78; N, 3.09;

Found: C, 81.84; H, 8.01; N, 3.06.

FAB: Calc. for  $C_{31}H_{35}NO_2$ : 453; Found: 453.

#### EXAMPLE 12

##### 17- $\beta$ -(3-Phenylbenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one

To a suspension of 258.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 932.0 mg of 3-bromobiphenyl in 2.0 ml of dry THF under  $N_2$ . The reaction was run in an ultrasonic bath at a temperature range of  $24-30^\circ C$ . To the well-agitated mixture was added dropwise 30 microliters of 1,2-dibromoethane/ $N_2$ . The concentration of the Grignard reagent was 4 mmoles in 10.0 ml of dry THF.

The steroid from Example 2, 205.0 mg (0.5 mmoles) was suspended in 2.0 ml of dry THF, cooled to  $-80^\circ C$  and the above prepared Grignard, 3.80 ml, was added via syringe to the steroidal suspension over 5-10 minutes/ $N_2$ . The reaction was allowed to proceed for 1 hour at  $-80^\circ C/N_2$  and then at  $-10^\circ C$  for an

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additional hour/ $N_2$ . The solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of  $NH_4Cl$  to pH=4. The organic layers were separated, washed 3 times with water, 3 times with saturated sodium chloride, dried over  $MgSO_4$ , filtered, and evaporated under vacuum. Crystallization from ethyl acetate afforded 122.84 mg of product. The material was purified on 20.0 g of silica gel column using 70:30 ( $CHCl_3$ -acetone) as eluant, to give a single spot material 117.0 mg of the above-titled compound, m.pt. 184-185°C.

Anal. Calcd. for  $C_{31}H_{35}NO_2$ :  
C, 82.08; H, 7.78; N, 3.09;  
Found: C, 82.28; H, 8.04; N, 2.98.  
FAB: Calcd. for  $C_{31}H_{35}NO_2$ : 453; Found: 453.

### EXAMPLE 13

#### Synthesis of 17-B-(4-Methylthiobenzoyl)- 4-aza-5- $\alpha$ -androst-1-en-3-one

To a suspension of 250.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 812.0 mg of p-bromophenyl methyl sulfide in 3.0 ml of dry THF under  $N_2$ . The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 40  $\mu$ l of 1,2-dibromoethane/ $N_2$ . The reaction was allowed to proceed for 1 to 1 1/2 hours at 28°C/ $N_2$ . The concentration of the Grignard reagent was 4.0 mmoles in 10 ml of dry THF.

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The steroid from Example 2, i.e. the pyridylthio ester, 205 mg, was suspended in 2.0 ml of dry THF, cooled to  $-80^{\circ}\text{C}$  and the above prepared Grignard was added via syringe to the steroidal suspension in 5-10 minutes/ $\text{N}_2$ . The reaction was allowed to proceed for 1 hour at  $-80^{\circ}\text{C}/\text{N}_2$  and then at  $-10^{\circ}\text{C}$  for an additional hour/ $\text{N}_2$ . The solution was diluted with 10.0 ml of methylene chloride, and quenched with saturated aqueous solution of  $\text{NH}_4\text{Cl}$  to pH=4. The organic layers were separated, washed 3 times with water; 3 times with saturated sodium chloride, dried over  $\text{MgSO}_4$ , filtered, and evaporated under vacuum to afford 105.0 mg of crude product.

The crude product was chromatographed on TLC (one plate, 20 cm x 20 cm x 20 cm x 1000  $\mu\text{m}$  silica gel) eluted with 80:20 ( $\text{CH}_2\text{Cl}_2$ -acetone) to afford 66.0 mg of single spot material. Crystallization from EtOAc afforded 45.0 mg of the above-titled compound, m.pt.  $286-287^{\circ}\text{C}$ .

FAB for  $\text{C}_{26}\text{H}_{33}\text{NO}_2\text{S}$  (Calcd.) 424; Found 424.

#### EXAMPLE 14

Synthesis of 17- $\beta$ -(4-methylsulfinylbenzoyl) and -  
(4-methylsulfonylbenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one

##### A. Oxidation

19.91 mg of the methylthio product from Example 13 was dissolved in 2.5 ml of  $\text{CH}_2\text{Cl}_2$ , cooled to  $0-(-2)^{\circ}\text{C}$  and was treated with a solution 9.6 mg of m-chloroperbenzoic acid in 1.0 ml of  $\text{CH}_2\text{Cl}_2$  over a period of 4 minutes. After stirring for 1 hour at  $0-(-2)^{\circ}\text{C}$ , the reaction was diluted with 10 ml.

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CH<sub>2</sub>Cl<sub>2</sub>. The layers were washed subsequently with 2.5% NaHCO<sub>3</sub>, H<sub>2</sub>O and saturated NaCl solutions. The organic layer was dried over MgSO<sub>4</sub> overnight, filtered and evaporated in vacuo to yield 17 mg product. Crystallization from EtOAc gave 11.8 mg of the above-titled compound, a solid, mp. 313-313.5°C (with dec.).

Anal. Calcd. for C<sub>26</sub>H<sub>33</sub>NO<sub>3</sub>S • 1/4H<sub>2</sub>O:

C, 70.31; H, 7.60; N, 3.15;

Found: C, 70.47; H, 7.70; N, 3.00.

FAB for C<sub>26</sub>H<sub>33</sub>NO<sub>3</sub>S (Calcd. 440); Found 440.

#### Sulfone

Fifteen percent (15%) of the corresponding sulfone, 17B-(4-methylsulfonyl benzoyl) derivative, was isolated by chromatography from the reaction as a byproduct. Recrystallized from EtOAc to yield a solid, mp. 279-279.5°C. Molecular weight by FAB showed 456; calculated 456.

Anal. for C<sub>26</sub>H<sub>33</sub>NO<sub>4</sub>S • 0.25 H<sub>2</sub>O

Calc: C, 67.87; H, 7.28; N, 3.04.

Found: C, 67.96; H, 6.72; N, 2.95.

#### EXAMPLE 15

Synthesis of 17-B-(4-acetoxymethylthiobenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one

Trifluoroacetic anhydride (165  $\mu$ l) was dissolved in 780  $\mu$ l of acetic anhydride and kept for 5 hours at room temperature (RT).

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To 300  $\mu$ l of the above solution of mixed anhydrides was added 34.15 mg pure sulfoxide from Example 14 with stirring. A few minutes later 54.0  $\mu$ l of 2,6-lutidine was added and the reaction was  
5 allowed to stir at RT/N<sub>2</sub> for 17 hours.

The liquid anhydrides were removed under reduced pressure and the remaining residue extracted (4 times with CHCl<sub>3</sub>). The CHCl<sub>3</sub> extracts were washed  
10 subsequently with dilute HCl; 5% NaHCO<sub>3</sub> solution, 3 times; 3 times with H<sub>2</sub>O; and finally with saturated NaCl solution, and then dried over MgSO<sub>4</sub> filtered and evaporated the solution to dryness in vacuo to yield 42.1 mg of crude product.

The crude product from Step A was purified  
15 by chromatography on silica gel using 95:5 (CHCl<sub>3</sub>-acetone) as eluant and then crystallizing the obtained solid from EtOAc to yield 17.8 mg of the above-titled compound as crystals, m.pt. 235-236°C (dec.).

20 Anal. Calcd. for C<sub>28</sub>H<sub>35</sub>O<sub>4</sub>NS • 1/4 H<sub>2</sub>O:  
C, 68.57; H, 7.40; N, 2.86;  
Found: C, 69.02; H, 7.39; N, 2.73.  
FAB for C<sub>28</sub>H<sub>28</sub>O<sub>4</sub>NS calcd.: 482; Found 482.  
The NMR (proton) was in agreement with  
25 the assigned product structure.

#### EXAMPLE 16

Synthesis of 17 $\beta$ -(4-mercaptobenzoyl)-4-aza-5 $\alpha$ -  
androst-1-en-3 one

30 40.0 mg of the acetoxy-methyl-thio derivative from Example 15 was suspended in 3.0 ml of isopropanol. The reaction mixture was flushed

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several times with  $N_2$ , and with vacuum, and the system kept under nitrogen atmosphere. To the above mixture was added 40.0 mg of  $K_2CO_3$  in 2.00 ml of water (free of oxygen) via syringe, and the

5 temperature of the reaction mixture was allowed to rise to  $80^\circ C$  under gentle reflux under slight vacuum for 10 minutes, and then under  $N_2$  for 1 hour. After 1 hour, the reaction mixture was a clear yellow solution. It was brought to R.T., cooled to  $0-5^\circ C$

10 and quenched with 2.5 N HCl acid/ $N_2$ . The reaction mixture was extracted 4 times with  $CH_2Cl_2$ . The organic layer was washed with  $H_2O$  4 times; 3 times with saturated salt solution, and finally dried over  $MgSO_4$ . Filtered and evaporated to dryness in vacuo

15 to yield 36.9 mg of crude product. The crude product was dissolved in 2.0 ml of  $CHCl_3$ , filtered through Teflon (Acrodisc CR) and purified by preparative HPLC on silica gel and eluted with 60:40 ( $CH_2Cl_2$ -acetone). Crystallization, from EtOAc

20 afforded a single spot material, 20.7 mg of the above-titled compound, m.pt.  $285-286^\circ C$ .

Anal. Calcd. for  $C_{25}H_{31}O_2NS$  .  $1/2 H_2O$ :

C, 72.19; H, 7.69; N, 3.24;

Found: C, 71.82; H, 7.43; N, 3.26.

25 FAB: Calcd. for  $C_{25}H_{31}O_2NS$ : 410; Found: 410.



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EXAMPLE 17Synthesis of 17-B-(4-Dimethylaminobenzoyl)-4-aza-5-a-androst-1-en-3-one

5 To a suspension of 291.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 800.0 mg of 4-bromo-N,N-dimethylaniline in 2.0 ml of dry THF under N<sub>2</sub>. The reaction was run in an ultrasonic bath at a temperature range of 24-30°C. To the well-agitated mixture was added dropwise 30 ml of 10 1,2-dibromoethane/N<sub>2</sub>. The reaction was allowed to proceed for 1 to 1 1/2 hours at 28°C/N<sub>2</sub>. The concentration of the Grignard reagent was 4.0 mmoles in 10.0 ml of dry THF.

15 The steroid from Example 2 (205 mg of pyridyl thioester) was suspended in 2.0 ml of dry THF, cooled to -80°C and the above Grignard 3.8 ml (3 equivalents) was added via syringe to the steroidal suspension over 5-10 minutes/N<sub>2</sub>. The reaction was allowed to proceed for 1 hour at -80°C/N<sub>2</sub> and then at 20 -10°C for an additional hour/N<sub>2</sub>. The solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of NH<sub>4</sub>Cl to pH=4. The organic layers were separated, washed 3 times with water 3 times with saturated sodium 25 chloride, dried over MgSO<sub>4</sub>, filtered, and evaporated under vacuum to afford 151.3 mg of crude product. Crystallization from ethyl acetate gave 124.5 mg of the above-titled compound, m.pt. 268.5-269°C.

30 FAB: Calcd. C<sub>27</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>: 421; Found: 421.  
The NMR (proton in CDCl<sub>3</sub>) confirmed the assigned structure.

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EXAMPLE 18General Procedure for Preparing Protected Silyl Derivatives

5 1.0 mole of phenol or its derivatives, or 1 mole of alcohol is treated with 1.5 liters of dry methylene chloride. To the clear solution is added dry 3.0 moles of imidazole/ $N_2$ . The clear solution is cooled to  $0^\circ C/N_2$ , and 2.0 moles of t-butyl dimethyl chlorosilane in 300.0 ml of dry methylene chloride is  
10 added dropwise at  $0^\circ C/N_2$ . Towards the end of the addition, precipitation occurs. The ice bath is removed, and the reaction is allowed to proceed overnight at R.T./ $N_2$ . Filter, wash the cake with cold  $CH_2Cl_2$  solution, and the solvent is evaporated  
15 in vacuo to afford crude product. The crude product was readily purified by filtering through a silica gel column. (1 gr. of crude product per 100 g of silica gel, using  $CH_2Cl_2$  as eluant) This method gives about 99% of pure silyl derivatives of phenols  
20 and alcohols.

EXAMPLE 19Synthesis of 17-B-(4-Hydroxybenzoyl)-4-aza-5- $\alpha$ -androst-1-ene-3-one25 A. Grignard Reaction

To a suspension of 1.22 g of dry activated magnesium chips in 20.0 ml of dry THF was added 5.6 g of 1-bromo-4-(tertiary-butyl dimethyl silyloxy)benzene (prepared from p-bromophenol by the General Procedure  
30 detailed above) in 10.0 ml of THF under  $N_2$ . The reaction was run in an ultrasonic bath at a temperature range of  $24-30^\circ C$ . To the well-agitated

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mixture was added dropwise 150  $\mu$ l-200  $\mu$ l of 1,2-dibromoethane/ $N_2$ . The reaction was allowed to proceed for 1-1 1/2 hours at 28°C/ $N_2$ . The concentration of the Grignard reagent formed was 19.5 mmols in 30.0 ml of dry THF.

The steroid from Example 2 (1.02 g, 2.49 mmols) was suspended in 20.0 ml of dry THF, cooled to -80°C and the above-prepared Grignard (11.5 ml) was added via syringe to the steroidal suspension in 5-10 minutes/ $N_2$ . The reaction was allowed to proceed for 1 hour at -80°C/ $N_2$ , and then at -10°C for an additional hour/ $N_2$ . The reaction solution was diluted with 10.0 ml of methylene chloride and quenched with a saturated aqueous solution of  $NH_4Cl$  to pH=4. Organic layers were separated, washed 3 times with  $H_2O$ , 3 times with saturated sodium chloride, dried over  $MgSO_4$ , filtered, and evaporated under a vacuum to a yellow color solid. Crystallization from ethyl acetate afforded 607 mg of product m.p. 248-249°C.

Anal. Calcd. for  $C_{31}H_{45}O_3NSi$ :

C, 73.32; H, 8.93; N, 2.75

Found: C, 73.27; H, 8.99; N, 2.75.

FAB: Found 508; Calc. 508.

#### B. Desilylation

Dissolved 1.3g of product from above step A in 20.0 ml of dry THF. Cooled to -5°C and added 437  $\mu$ l of glacial acetic acid/ $N_2$ . To the cold solution at -5°C was added via syringe 3.0 ml tetra-n-butylammonium fluoride dropwise under  $N_2$  atmosphere. Allowed the reaction to proceed under stirring for 1

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1/2-2 hours at 0° to -5°C/N<sub>2</sub>. The reaction mixture was poured into a 2-layer mixture of ethyl acetate/sodium bicarbonate saturated solution at 0°C. The water layer was separated and further  
5 extracted with EtOAc 3 times and with CH<sub>2</sub>Cl<sub>2</sub> (3 times).

The organic layers were combined, washed 3 times with H<sub>2</sub>O, 1 time with saturated sodium chloride solution, and dried over MgSO<sub>4</sub>, filtered and  
10 evaporated to dryness under vacuum. The crude product was crystallized from ethyl acetate to afford 977.9 mg, and further recrystallized from methanol to afford 842.3 mg of the above-titled product, m.pt. 296-297°C.

15 Anal. Calcd. for C<sub>25</sub>H<sub>31</sub>NO<sub>3</sub>.1/3 H<sub>2</sub>O:

C, 75.15; H, 7.98; N, 3.51.

Found: C, 75.13; H, 7.76; N, 3.54.

(Mass Spec.) FAB: Found 394; Calcd. 394.

20 EXAMPLE 20

17-B-(3,5-dimethyl-4-hydroxybenzoyl)-4-aza-5α-androst-1-ene-3-one

A. Preparation of Grignard Reagent

25 To a suspension of 260.0 mg of dry activated magnesium chips in 6.0 ml of dry THF was added 628.0 mg of 1-bromo-3,5-dimethyl-4-tertiary-butyl-dimethyl-silyloxybenzene (prepared from 4-bromo-2,6-dimethylphenol by the General Procedure described  
30 above) in 4.0 ml of THF/N<sub>2</sub>. The reaction was conducted in an ultrasonic bath at a temperature range of 24°-30°C. To the well-agitated mixture was

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added dropwise 40  $\mu$ l of 1,2-dibromoethane/ $N_2$ . The reaction was allowed to proceed for 2 hours/ $N_2$ . The concentration of the Grignard reagent thus formed was 2 mmoles in 10.0 ml of dry THF.

5           The steroid from Example 2 (205.0 mg (0.5 mmoles) was suspended in 3.0 ml of dry THF, cooled to  $-80^\circ\text{C}$ , and 7.5 ml (1.50 millieq.) of the above-prepared Grignard was introduced via syringe to the steroidal suspension over a period of 5-10  
10 minutes/ $N_2$ . The reaction was allowed to proceed for 1 hour at  $-80^\circ\text{C}/N_2$  and then at  $-10^\circ\text{C}$  for additional hour/ $N_2$ .

          The reaction was quenched with 1N HCl, and then diluted with chloroform. The organic layers  
15 were combined, washed 3 times with  $H_2O$ , 3 times with saturated sodium chloride and dried over  $MgSO_4$ , filtered and concentrated in vacuo. The crude residue was washed with ether to afford 121.7 mg of product.

20           The crude product was dissolved in 70:30 ( $CHCl_3$ -acetone), filtered through Teflon (Acrodisc CR) and purified by preparative HPLC (Waters Prep-pak) on silica gel and eluted with 70:30 ( $CHCl_3$ -acetone).

          The major component was recrystallized from  
25 ethyl acetate to give 52.0 mg of product m.pt  $245-245.5^\circ\text{C}$ .

Anal. Calcd. for  $C_{33}H_{49}O_3NSi$ :

C, 73.96; H, 9.23; N, 2.61

Found: C, 74.06; H, 9.33; N, 2.64

30 (Mass Spec.) FAB: Found: 536; Calc.: 536

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### B. Deblocking the Silyl Derivative

Dissolved 54.0 mg of the above product from A in dry THF (1.3 ml). The clear solution was cooled to 0°C, and 29 µl of glacial HOAc was added via syringe/N<sub>2</sub>. To the above solution was added dropwise 172 µl of tetra-n-butylammonium fluoride at 0°C dropwise via syringe/N<sub>2</sub>. Allowed the reaction to proceed at 0°C/N<sub>2</sub> for 1 1/2 hours. The reaction mixture was poured into ice/saturated NaHCO<sub>3</sub> solution and EtOAc. Stirred for several minutes. Allow the layers to separate, and the H<sub>2</sub>O layer was extracted 3 times with EtOAc and 3 times with CHCl<sub>3</sub>.

Combined the organic layers and washed 3 times with H<sub>2</sub>O, then 3 times with saturated NaCl, and then dried over MgSO<sub>4</sub>, filtered and evaporated to dryness in vacuum to afford 52.2 mg.

The product was crystallized from EtOAc to give 22.5 mg of the above-titled product m.pt 305-306°C.

Calc. for C<sub>27</sub>H<sub>35</sub>O<sub>3</sub>N·H<sub>2</sub>O:

C, 73.77; H, 8.49; N, 3.10.

Found: C, 73.62; H, 7.90; N, 3.44.

(Mass Spec.) FAB: Calc:422; Found: 422

### EXAMPLE 21

Synthesis of 17-B-(4-Methoxybenzoyl)-4-aza-5-α-androst-1-ene-3-one

#### A. Grignard Reaction

To a suspension of 258.0 mg of dry activated Mg chips in 8.0 ml of THF/N<sub>2</sub> was added 748.0 mg p-bromoanisole in 2.0 ml of dry THF. The reaction

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was run in an ultrasonic bath at a temperature range of 24-30°C/N<sub>2</sub>. To the well-agitated mixture was added dropwise 30.0 µl of 1,2-dibromoethane as a catalyst. The reaction was allowed to progress for 1-2 hours at 28°C. The formed Grignard reagent had a concentration of 4 mmoles in 10.0 µl of dry THF.

The steroid from Example 2 (205.0 mg (0.50 mmol) was suspended in 2.0 ml of THF, cooled to -78°C and the above-prepared Grignard reagent (3.75 ml; 14 milliequivalents) was added via syringe to the steroidal suspension over 5-10 minutes/N<sub>2</sub> and then at -10°C for an additional hour/N<sub>2</sub>. The resulting reaction mixture was a clear solution, which was cooled to 0-5°C, diluted with chloroform and quenched with 1N HCl acid. The organic layers were separated, washed with H<sub>2</sub>O 2 times, followed with saturated NaCl solution, dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo. The crude product was washed with ether, and crystallized from EtOAc to give 110 mg of product m.pt 305-306°C.

Further purification was carried out by chromatographic isolation on a TLC. plate, (20 cm x 20 cm x 1000 µm), using as eluant, 70:30 (CHCl<sub>3</sub>: acetone). Recrystallization from EtOAc yielded 78.56 mg of the above-titled product, m.pt 305-306°C (dec.). (Mass Spec) FAB: Calcd., 408; Found 408.

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EXAMPLE 22

Synthesis of 17- $\beta$ -(3-hydroxybenzoyl)-4-aza-5 $\alpha$ -  
androst-1-ene-3 one

5     A. Preparation of Grignard Reagent

          To a suspension of 230.0 mg of dry activated  
Mg chips in 2.0 ml of dry THF was added 722.4 mg of  
1-bromo-3-tertiary-butyl dimethyl-silyloxybenzene  
10     (prepared from 3-bromophenol by the General Procedure  
described above) in 8.0 ml of dry THF/N<sub>2</sub>. The  
reaction was run in an ultrasonic bath at a temper-  
ature range of 24-30°C/N<sub>2</sub>. To the well-agitated  
mixture was added dropwise 20.0  $\mu$ l of 1,2-  
15     dibromoethane/N<sub>2</sub>. Allowed the reaction to progress  
for 2 1/2 hours at 28°C/N<sub>2</sub>. The formed Grignard  
reagent had a concentration of 2.52 mmoles in 10.0 ml  
of dry THF.

          The steroid from Example 2 (205.0 mg (0.5  
mmoles) was suspended in 2.0 ml of THF, cooled to  
20     -78°C and the above-prepared Grignard reagent (6.0  
ml, (1.5 milliequivalents) was added via syringe to  
the steroidal suspension over 5-10 minutes/N<sub>2</sub>, and  
then stirred for an additional hour at -10°C/N<sub>2</sub>. The  
clear reaction mixture was quenched at 0 to -5°C with  
25     1N HCl acid for 10.0 minutes and diluted with CHCl<sub>3</sub>.  
The combined organic layers were washed 3 times with  
H<sub>2</sub>O, 3 times with saturated NaCl, and then dried over  
MgSO<sub>4</sub>, filtered and concentrated in vacuo to afford  
crude product. The product was purified on silica  
30     gel column and was eluted with 70:30 (CHCl<sub>3</sub>-



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acetone). The desired product amounted to 58.0 mg, as the silyl derivative, 17B-(3-tertiary-butyl-dimethylsilyloxybenzoyl)-4-methyl-4-aza-5 $\alpha$ -androst-1-en-3-one.

5

B. Deblocking

57.6 mg of the above silyl derivative was dissolved in 3.0 ml of dry THF. The solution was cooled to 0°C, and 20  $\mu$ l of glacial acetic acid was introduced via syringe. To the clear solution was added 130.0  $\mu$ l of (n-butyl)<sub>4</sub>NF via syringe, and allowed the reaction to proceed for 1 hour/N<sub>2</sub> at 0°C. The reaction mixture was poured into EtOAc/NaHCO<sub>3</sub> sat. solution @ 0°C. The water layer was separated, extracted 3 times with EtOAc and then 3 times with chloroform. The organic layers were combined and washed 3 times with H<sub>2</sub>O, 3 times with saturated NaCl solution; dried over MgSO<sub>4</sub>, filtered and evaporated in vacuo to give 57.11 mg of crude product. The crude product was chromatographed by TLC (one plate, 20 cm x 20 cm x 250  $\mu$ m silica gel), eluted with 70:30 (CHCl<sub>3</sub>-acetone) to afford 44.5 mg of the above-titled product. Recrystallization from EtOAc gave 29.30 mg m.pt 279-280°C.

25

Anal. Calcd. for C<sub>25</sub>H<sub>31</sub>NO<sub>3</sub>: 8H<sub>2</sub>O:

C, 73.60; H, 8.06; N, 3.43.

Found: C, 73.26; H, 8.22; N, 3.28.

(Mass Spec.) FAB: Calcd: 394; Found 394.

30

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EXAMPLE 23Synthesis of 17- $\beta$ -(4-hydroxymethyl-benzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-oneA. Preparation of Grignard solution

5 To a suspension of 100.0 mg (4 mmoles) of dry activated Mg chips in 5.0 ml of dry THF/N<sub>2</sub>, was added 753.0 mg (2.5 mmoles) of 1-bromo-4-tertiary-butyl dimethyl silyloxy methyl benzene (prepared from 4-bromobenzyl alcohol by the General  
10 Procedure described above). The reaction was conducted in an ultrasonic bath at a temperature range of 24-30°C/N<sub>2</sub>. To the well-agitated mixture was added 20  $\mu$ l of 1,2-dibromoethane/N<sub>2</sub>. Allowed the reaction to progress for 2 hours at 28°C/N<sub>2</sub>. The  
15 concentration of formed Grignard was 2.5 mmoles in 5.0 ml of dry THF.

B. Grignard Reaction

20 The steroid from Example 2 (205.0 mg (0.5 mmoles) was suspended in 2.0 ml of THF, cooled to -78°C, and the above-prepared Grignard (3.0 ml, 3.75 milliequivalents) was introduced via syringe into the steroidal suspension over 5-10 minutes/N<sub>2</sub>. Allowed the reaction to progress for 1 hour at -80°C/N<sub>2</sub>, and  
25 then for an additional hour at -10°C/N<sub>2</sub>. The clear reaction solution was quenched with saturated NH<sub>4</sub>Cl at 0° to -5°C, and then diluted with CH<sub>2</sub>Cl<sub>2</sub>. The organic layers were separated and washed 3 times with water, 3 times with saturated NaCl, dried over MgSO<sub>4</sub>,  
30

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filtered and evaporated in vacuo to dryness. Crude product was crystallized from EtOAc to give 137.8 mg of silyl product.

(Mass Spec.) FAB: Calcd for  $C_{30}H_{41}O_3NSi$ : 521.75  
Found: 522.0.

C. Deblocking of Silyl Derivative

The product from Step B above (23.67 mg) was dissolved in 0.5 ml of THF and 0.5 ml of MeOH and cooled to  $0^{\circ}C/N_2$ . To the cold solution was added 10  $\mu$ l of concentrated sulfuric acid (98%). The reaction was stirred for 45 minutes at  $0^{\circ}C/N_2$ . To the cold solution at  $0^{\circ}C$  was slowly added a saturated solution of  $NaHCO_3$  and chloroform. Extracted 3 times with  $CHCl_3$ . The organic layers were washed 3 times with water, 3 times with saturated NaCl, solution dried over  $MgSO_4$ , filtered and evaporated to dryness in vacuo, to afford 10.18 mg. After chromatography on a TLC plate (elution with 1:1  $CHCl_2$ : acetone) The crude product was crystallized from EtOAc to give 6.0 mg of the above-titled product, m.pt  $318-320^{\circ}C$ .

Anal. Calcd. for  $C_{26}H_{33}O_3N.1/3H_2O$ :

C, 75.41; H, 7.94; N, 3.38.

Found: C, 75.61; H, 7.84; N, 3.12.

(Mass Spec.) FAB: Calc.: 408; Found: 408

30

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EXAMPLE 24

Synthesis of 17-B-(4-Carboxybenzoyl)-4-aza-5 $\alpha$ -androst-1-en-3-one

A. Oxidation

5                   90.2 mg of the product from Example 23 was  
dissolved in 2.63 ml of glacial acetic acid and to  
the clear solution was added 69.0 mg of CrO<sub>3</sub>  
(previously dried over P<sub>2</sub>O<sub>5</sub> at R.T. for 2 days  
10                   in vacuo). After stirring overnight, the reaction  
mixture was diluted with water and allowed to age  
overnight in the refrigerator. The reaction mixture  
was filtered and the mother liquor and washes were  
extracted overnight using a liquid-liquid extractor,  
(H<sub>2</sub>O-EtOAc) under reflux conditions. The organic  
15                   layer was dried over MgSO<sub>4</sub>, filtered and evaporated  
in vacuo. The residue was dissolved in hot MeOH,  
filtered and evaporated in vacuo to afford a product  
weighing 32.0 mg.

FAB: Calc. for C<sub>26</sub>H<sub>31</sub>O<sub>4</sub>N: 422.0;

20                   Found: 422.

B. Purification

The above free acid was purified by  
dissolving the above product in 1N sodium hydroxide  
25                   solution. The clear solution was extracted 3 times  
with EtOAc. The aqueous basic solution was cooled  
and acidified with 1N HCl acid dropwise to pH=4 with  
stirring. The reaction mixture was allowed to age  
for 1 hour at 0°C. It was filtered and the residue  
30                   was washed with cold water. Dried overnight to 100°C  
in vacuum <0.2 mm pressure.

Yield of the above-titled free acid was 9.85 mg.

FAB: Calc. for C<sub>25</sub>H<sub>31</sub>O<sub>4</sub>N: 422; Found 422.

NMR analysis indicated the product to be an acid.

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C. Sodium Salt of Above Acid

4.9 mg of the above product acid B was dissolved in 2.0 ml of hot methanol. To the clear solution, was added 11.6  $\mu$ l of 1N NaOH(aq). To  
5 solution after methanol evaporation in vacuo, was added water to reach pH 7.21. The aqueous solution was freeze dried to give 6.3 mg of the sodium salt of the above-titled product.

10

EXAMPLE 25

Synthesis of 17- $\beta$ -(4-hydroxyethylbenzoyl)-4-aza-  
5 $\alpha$ -androst-1-en-3-one

A. Grignard Reagent

15 To a suspension of 252 mg of dry activated Mg chips in 10.0 ml of dry THF was added 1.26 g (4 mmoles) of 1-bromo-4 tertiary-butyl dimethyl silyloxy ethyl benzene (prepared from 2-(p-bromophenyl) ethanol by the General Procedure described above). The  
20 reaction mixture was vigorously stirred using an ultrasonic vibrator/N<sub>2</sub>. To the well-agitated mixture was added 40  $\mu$ l of 1,2-dibromoethane to catalyze the above reaction. Allowed the reaction to progress for  
25 3 1/2-4 hours/N<sub>2</sub>. The concentration of formed Grignard reagent was 4 mmoles in 10 ml of THF.

B. Grignard Reaction

205.0 mg (0.5 mmoles) of the aza-steroid of Example 2 was suspended in 2.0 ml of dry THF/N<sub>2</sub>,  
30 cooled to -80°C, and the above-prepared Grignard (3.75 ml, 1.5 milliequivalents) via syringe was introduced into the steroidal suspension over 5-10

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minutes/ $N_2$ . The reaction was run at  $-80^\circ C$  for 1 hour/ $N_2$  and then for an additional hour at  $-10^\circ C$ . The reaction was quenched with a saturated solution of  $NH_4Cl$  at  $0-5^\circ C$  and diluted with 10.0 ml of  $CH_2Cl_2$ . The organic layers were washed with water (3 times), saturated  $NaCl$  solution (3 times), dried with  $MgSO_4$ , filtered and evaporated in vacuo to dryness. The crude product was crystallized from EtOAc overnight to give 152.0 mg of product m.pt.  $233-234^\circ C$ .

Anal. Calcd. for  $C_{33}H_{49}O_3NSi:1/4 H_2O$ :

C, 73.55; H, 9.18, N, 2.59.

Found: C, 73.45; H, 8.94; N, 3.21

FAB: Calc. 536; Found: 536

### 15 C. Desilylation

70.8 mg of product from Step B, was dissolved in 1.45 ml of methanol and 1.45 ml of THF. The solution was cooled to  $0-5^\circ C$  and 29  $\mu l$  of conc.  $H_2SO_4$  was added via syringe under  $N_2$ . The reaction was allowed to proceed for 45 minutes/ $N_2$ . The reaction was carefully quenched at  $0^\circ C$  with a saturated solution of  $NaHCO_3$ , and extracted 3 times with  $CH_2Cl_2$ . The organic layers were separated, washed with water (3 times), then with saturated  $NaCl$  solution, dried over  $MgSO_4$ , filtered and evaporated in vacuo to give 43.0 mg of crude product. The crude product was placed on a column of silica gel and was

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eluted with 1:1 acetone-CH<sub>2</sub>Cl<sub>2</sub>. The isolated product was crystallized from anhydrous methanol to afford 20.0 mg of the above-titled product m.pt 292-293°C with dec.

5        Anal. Calcd. for C<sub>27</sub>H<sub>35</sub>O<sub>3</sub>N.1/4 H<sub>2</sub>:  
              C, 75.31; H, 8.25; N, 3.25.  
              Found: C, 75.49; H, 8.29; N, 3.45.  
              FAB:    Calcd 422; Found 422.

10

EXAMPLE 26

Synthesis of 17-B-(4-carboxymethylbenzoyl)-4-aza-5α-androst-1-en-3-one

---

A. Oxidation

15        13.0 mg of the product from Example 25 was dissolved in 1 ml of glacial acetic acid. To the clear solution was added 10.0 mg of CrO<sub>3</sub> (previously dried over P<sub>2</sub>O<sub>5</sub> in vacuum at R.T.). Allowed the reaction to progress overnight at R.T., and then at  
20        0°C for 48 hours. The addition of 7.0 ml of water caused the product to crystallize overnight in a refrigerator. The crude product was isolated, washed with cold water and dried in a vacuum at 110°C below 1 mm pressure.

25        The dried crude product was dissolved in IN sodium hydroxide and the basic solution was extracted 3 times with methylene chloride (The organic layers were separated, and the aqueous basic solution was cooled and acidified with 1.5 N hydrochloric acid.  
30        The precipitate was filtered, washed with water dried at 110°C under vacuum at 0.1 mm pressure.

Yield of above-titled product=7.0 mg.

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FAB Calc.  $C_{27}H_{33}O_4N$ : 436; Found 436.EXAMPLE 27

Synthesis of 17- $\beta$ -(3,4-dihydroxybenzoyl)-4-aza-5 $\alpha$ -  
androst-1-en-3-one

A. Grignard

To a suspension of 258.5 mg of dry activated magnesium chips in 10.0 ml of dry THF, was added 482 mg. of 4-bromo-1,2-methylenedioxybenzene/ $N_2$ . (The starting material is commercially available from Aldrich Chemical) The reaction was conducted in an ultrasonic water bath at a temperature range of 24°-30°C. To the well-agitated mixture was added 40  $\mu$ l of 1,2-dibromoethane as a catalyst/ $N_2$ , and the reaction was allowed to progress for 1 1/2-2 hours at 28°C/ $N_2$ . The concentration of the formed Grignard reagent was 3.75 mmoles in 10 ml of dry THF.

The steroid from Example 2 (410 mg, 1mmole) was suspended in 4.0 ml of dry THF/ $N_2$  and cooled to -80°C and 8.0 ml of the above-prepared Grignard (3.04 milliequivalents) was added via syringe to the steroidal suspension/ $N_2$  over a period of 5-10 minutes. The reaction was allowed to proceed for 1 hour at -80°C, and then at -10°C for an additional hour/ $N_2$ . The reaction mixture was diluted with  $CH_2Cl_2$ , and then quenched with 1N HCl at -5°C.

The organic layers were collected and washed with water 3 times, saturated NaCl solution 3 times, dried over  $MgSO_4$ , filtered and evaporated in vacuo to



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dryness. Purification of the crude product was carried out on 50.0 g of silica gel using as eluant 1:1(CH<sub>2</sub>Cl<sub>2</sub>-acetone) to give 347.0 mg.

FAB showed 422; Calcd. 422.

5           62.4 mg of the above product was crystallized from EtOAc to afford 11.39 mg of product m.pt.324-325°C.

Anal. Calcd. for C<sub>26</sub>H<sub>31</sub>O<sub>4</sub>N .3/4 H<sub>2</sub>O:

C,71.78; H,7.53; N,3.22.

10          Found: C,71.90; H,7.54; N,3.25.

FAB for C<sub>26</sub>H<sub>31</sub>O<sub>4</sub>N showed 422; Calcd: 422.

B. Cleavage of Methylene Dioxylan Group

15           70.0 mg of the product from Step A was dissolved in dry 25.0 ml of 1,2-dichloroethane at R.T./N<sub>2</sub>. The solution was allowed to cool to -10°C, and 1.03 ml of BBr<sub>3</sub> (1.0 M solution in dichloromethane) was added dropwise under N<sub>2</sub> atmosphere. The reaction was allowed to proceed at  
20          R.T. for 3 1/2-4 hours/N<sub>2</sub>. After 4 hours/N<sub>2</sub>, the reaction was cooled to (-10°C) and quenched with 10.0 ml of methanol for 10 minutes at 0°C, and then gradually the temperature was allowed to rise to R.T./N<sub>2</sub>. The reaction mixture was evaporated in  
25          vacuo to dryness. The residue was extracted 3 times with EtOAc. The organic layers were washed with water 3 times, 2 times with saturated NaHCO<sub>3</sub> solution, 3 times with water and finally with a  
30          saturated solution of NaCl. The organic layers were dried over magnesium sulfate, filtered and concentrated in vacuo. The crude material was

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chromatographed on 2 silica gel plates, (20 cm x 20 cm x 20 cm x 250  $\mu$ m) eluted with 1:1 (acetone - methylene chloride). Recrystallization from EtOAc afforded 5.0 mg of the above-titled product m.p. 222-222.5°C.

Anal. Calcd. for  $C_{25}H_{31}O_4N \cdot 1/2 H_2O$ :

C, 71.78; H, 7.66; N, 3.35.

Found: C, 71.71; H, 7.71; N, 3.33.

FAB: Calcd. for  $C_{25}H_{31}O_4N$ : 410; Found 410.

#### EXAMPLE 28

Synthesis of 17-B-(2 methoxybenzoyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one

##### A. Grignard

To a suspension of 258.0 mg of dry activated magnesium chips in 8.0 ml of dry THF was added 771.0 mg of o-bromoanisole in 2.0 ml of dry THF/ $N_2$ . The reaction was conducted in an ultrasonic water bath at a temperature range of 24-30°C. To the well-agitated mixture was added 30  $\mu$ l of 1,2-dibromoethane/ $N_2$ , and the reaction was allowed to progress for 2 hours at 28°C/ $N_2$ . The concentration of the formed Grignard reagent was 4 mmoles in 10.0 ml of dry THF.

The steroid from Example 2 (205 mg, 0.5 mmoles) was suspended in 2.0 ml of dry THF/ $N_2$ , cooled to -79°C, and 4.0 ml of the above-prepared Grignard (1.6 milli-equivalents) was added via syringe to the steroidal suspension/ $N_2$  over a period of 5-10 minutes. The reaction mixture was allowed to proceed

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for 1 hour at  $-80^{\circ}\text{C}$ , and then at  $0-2^{\circ}\text{C}$  for an additional hour/ $\text{N}_2$ . The reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  and then quenched with 1N HCl solution at  $0^{\circ}\text{C}$ .

5           The organic layers were combined, washed 3 times with water, 3 times with saturated NaCl solution; and dried over  $\text{MgSO}_4$ . Filtered and evaporated in vacuum to dryness. The crude material was crystallized from EtOAc to give 124.5 mg of  
10       product m.pt  $228-230^{\circ}\text{C}$ . Purification on silica gel column using 70:30 ( $\text{CHCl}_3$ -acetone) gave a single spot material in a yield of 83.0 mg m.pt.  $241-241.5$ .

Anal. Calcd. for  $\text{C}_{26}\text{H}_{33}\text{O}_3\text{N}$ :

C, 76.91; H, 8.19; N, 3.45

15       Found: C, 76.36; H, 8.26; N, 3.35.

FAB calcd. for  $\text{C}_{26}\text{H}_{33}\text{O}_3\text{N}$ : 406; Found: 406.

#### B. Cleavage of Methoxy Group

12.7 mg (0.03 mmoles) of the product from  
20       Step A was dissolved in 5.0 ml of dry methylene chloride/ $\text{N}_2$ . To clear solution at  $-79^{\circ}\text{C}/\text{N}$ , was added 50  $\mu\text{l}$  of 1 mmole/ml of  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  via syringe dropwise. Allowed the reaction to proceed at R.T. overnight/ $\text{N}_2$  with rapid stirring. Next day,  
25       a clear yellow solution was obtained. The reaction mixture was cooled to  $0-2^{\circ}\text{C}$  and quenched with water, to hydrolyze excess of  $\text{BBr}_3$ . The organic phase was washed 3 times with dilute sodium hydroxide, 3 times with water, 3 times with dilute HCl, 3 times with  
30       water, 3 times with saturated NaCl solution, and dried the organic layer over  $\text{MgSO}_4$ . Filtered, concentrated in a vacuum to dryness. The crude

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product crystallized from EtOAc to afford 7.0 mg of a pure single spot material being 17-B-(2-hydroxy-methyl-benzoyl)-4-aza-5- $\alpha$ -androst-1-en-3-one.

FAB for  $C_{25}H_{31}NO_2$ ; Calcd: 394; Found: 394.

5

#### EXAMPLE 29

##### 17B( $\alpha$ -hydroxybenzyl)-4-aza-5 $\alpha$ -androst-1-ene-3-one

570 milligrams of 17B-benzoyl-4-aza-5 $\alpha$ -androst-1-ene-3-one (prepared from the thiopyridyl ester of Example 2 and commercially available phenyl magnesium bromide, analogously via the procedure in Example 5, to produce the 17-benzoyl derivative, mp. 295-296°C crystallized from EtOAc) was suspended in 80 ml of anhydrous isopropanol. To the suspension was added 500.0 mg of  $NaBH_4$  in 5 portions. When all the hydride was added, 20.0 ml of dry THF was carefully added, so that the reaction mixture became a clear solution. Allowed the reaction to proceed at R.T./ $N_2$  overnight. The reaction was quenched carefully with 1N HCl, and allowed to stir under  $N_2$  for an additional hour at R.T. It was then diluted with water, and extracted 3 times with  $CHCl_3$ . The organic layers were combined, washed 3 times with  $H_2O$ ; 3 times with saturated NaCl solution, and dried over  $MgSO_4$ . Filtered and evaporated to a white solid weighing 495.0 mg.

25

The crude material was crystallized from EtOAc to afford 349.5 mg of material. Further purification on a silica gel column, using as eluant,

30

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70:30 (CHCl<sub>3</sub>-acetone) gave a single spot material, 221 mg, of the above-titled compound, m.pt 296-297°C.

Anal. Calcd. for C<sub>25</sub>H<sub>33</sub>NO<sub>2</sub>:

C, 79.17; H, 8.78; N, 3.70.

5 Found: C, 79.24; H, 8.85; N, 3.48.

FAB Calcd. for C<sub>25</sub>H<sub>33</sub>NO<sub>2</sub>: 380; Found: 380.

### EXAMPLE 30

#### 17β-hydroxymethyl-4aza-5α-androst-1-ene-3-one

10 500.0 mg of S-2-pyridyl-3-oxo-4-aza-5α-androst-1-ene-3 one (Example 2) was dissolved in 40.0 ml of dry THF at R.T./N<sub>2</sub>. The solution was cooled to -78°C/N<sub>2</sub> and 5.5 ml of 1 M dibutyl aluminium hydride  
15 in THF was slowly added via syringe to the solution, with rapid stirring. Allowed the reaction to proceed at -76 to -78°C for half an hour under N<sub>2</sub>. The temperature was gradually brought to R.T. and the reaction mixture kept for 2-1/2 hours/N<sub>2</sub>. The  
20 reaction was then quenched at 0° to 5°C with 2N HCl acid, and then diluted with CHCl<sub>3</sub>. The organic layers were separated, washed with H<sub>2</sub>O 3 times, then with saturated NaCl solution, and finally dried over MgSO<sub>2</sub>. Filtered, and the organic phase was  
25 evaporated under vacuum to give 216.0 mg of crude product.

The crude product was chromatographed on 20.0 g of E.M. silica gel column, using 70:30(CHCl<sub>3</sub>-acetone) as eluant.

30 Yield of single spot material was 126.3 mg of the above-titled compound, m.pt. 271-271.5°C.

Calcd. for C<sub>19</sub>H<sub>29</sub>O<sub>2</sub>N: FAB 304; Found 304.

NMR in CDCl<sub>3</sub> confirmed the above structure.

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EXAMPLE 3117B-Formyl-4-aza-5 $\alpha$ -androst-1-ene-3-one

5 Into a 100.0 ml dry flask was placed 1.3 ml of oxalyl chloride (2 M in CH<sub>2</sub>Cl<sub>2</sub>) with 50.0 ml of dry CH<sub>2</sub>Cl<sub>2</sub>/N<sub>2</sub>. The above solution was cooled to -78°C and 338  $\mu$ l of DMSO was added dropwise via syringe/N<sub>2</sub>. The mixture was stirred at -78°C/N<sub>2</sub> for 30 minutes, and a solution of above-prepared alcohol from Example 15, i.e. 17B hydroxymethyl-4-  
10 aza-5 $\alpha$ -androst-1-ene-3-one (256.9 mg in 15.0 ml of dry CH<sub>2</sub>Cl<sub>2</sub>/N<sub>2</sub> was added via syringe. The reaction was allowed to progress for one hour at -78°C/N<sub>2</sub>. After an hour at -78°C, was added 1 ml of dry triethylamine at a rapid rate. Reaction was raised  
15 slowly to R.T./N<sub>2</sub> with stirring, the resulting yellow solution was then poured into 50.0 ml of cold water. The organic layers were washed with a saturated solution of NaHCO<sub>3</sub>, and then with a saturated solution of NaCl. Dried over MgSO<sub>4</sub>, evaporated the  
20 solvent under vacuum to give 172.4 mg of crude product. The crude product was chromatographed on 60.0 g silica gel column using 70:30 (CHCl<sub>3</sub>-acetone), to give a single spot material. Crystallization from EtOAc afforded the above-titled compound, 37.7 mg,  
25 m.pt. 258-259°C.

EXAMPLE 32Synthesis of diastereoisomeric 17B( $\alpha$ -hydroxybenzyl)-4-aza-5 $\alpha$ -androst-1-ene-3-ones

30 26.3 of above-prepared formyl derivative (from Example 31) was dissolved in 7.0 ml of dry THF/N<sub>2</sub>. The solution was cooled to -78°C/N<sub>2</sub>, and 131

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5  $\mu$ l of phenyl magnesium bromide (Aldrich reagent)  
0.393 milliequivalents) in dry THF was added dropwise  
via syringe/ $N_2$ . Allowed the reaction to proceed for  
1 hour/ $N_2$  at  $-78^\circ\text{C}$  and then at R.T. for addition  
hour/ $N_2$ .

The reaction was quenched at  $0-5^\circ\text{C}$  with 2.5N  
HCl, and then diluted with  $\text{CHCl}_3$ . Organic layers  
were separated, washed 3 times with water; 3 times  
with saturated NaCl solution, dried over  $\text{MgSO}_4$ .  
10 Filtered and evaporated in vacuum to dryness to  
afford 28.6 mg of crude product. Analysis of the NMR  
spectra and peak heights from HPLC indicated this  
product to be a 1:1 mixture of diastereoisomers.  
The crude product was filtered through a  $1\ \mu\text{m}$  Teflon  
15 filter and purified by HPLC on a Whitman Portisil 10  
column using 70:30( $\text{CHCl}_3$ -acetone). The FAB mass  
spectrum indicated the same  $M^+ + 1$  for both isomers,  
being 380 mass units. The faster eluting isomer,  
m.pt.  $289-289.5^\circ\text{C}$ , was crystallized from EtOAc and  
20 showed a single spot material on TLC.

Anal. Calcd. for  $\text{C}_{25}\text{H}_{33}\text{NO}_2 \cdot 1/4\ \text{H}_2\text{O}$ ;

C, 78.39; H, 8.81; N, 3.65.

Found: C, 78.11; H, 8.65; N, 3.58.

25 The slower eluting isomer, m.pt.  $300-301^\circ\text{C}$   
showed a single spot material on TLC. The faster  
isomer showed by NMR( $\text{CDCl}_3$ ):  $\text{CH}_3$  at C-18 was  
deshielded (0.89 $\delta$ ) as compared to the slower isomer  
 $\text{CH}_3$  at C-18 at (0.69 $\delta$ ). The benzylic proton for the  
30 faster isomer was also deshielded (4.5 $\delta$ ) versus

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(4.958). The olefinic proton at C-1 showed deshielding effects for the faster isomer at (6.818) to (6.628). From the above data, the two isomers showed distinctly different physical properties.

5

CHAPTER 3EXAMPLE 1

10

Preparation of 4-(2-(11-carboxyundecanoylamino)-phenoxy)butyric acid

Step A: Ethyl 4-(2-nitrophenoxy)butyrate(3)

15

To a stirred solution of 2-nitrophenol (1.4 g, 10 mM) and ethyl 4-bromobutyrate (2.1 g, 1.57 mL, 11 mM) in 35 mL of dry acetone is added 2 g (14.5 mM) of anhydrous, ground potassium carbonate. The resultant colored mixture is then heated under a nitrogen atmosphere at gentle reflux until the color due to the phenol anion has dissipated and a yellow mixture remains. Concentration of the cooled and filtered mixture yields an oil which on flash chromatography (silica gel, ethyl acetate/hexane or methylene chloride as eluant) yields 2.4 g (96% yield) of the title compound (3) as an oily liquid.

20

25

When substituted ortho-nitrophenols are used in place of 2-nitrophenol in the above example, the corresponding substituted 2-nitrophenoxybutyrate is obtained. Likewise, when ethyl 4-bromobutyrate is replaced by other halo esters, the corresponding 2-nitrophenoxyalkanoate is obtained.

30



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Step B: Ethyl 4-(2-aminophenoxy)butyrate (4)

5 A solution of 3 (1.27 g, 5.0 mM) in 15 mL ethyl acetate containing 200 mg of 5% palladium on carbon is reacted in a hydrogen atmosphere (40 psig.) at room temperature until hydrogen uptake ceases. The mixture is then filtered and concentrated in vacuo to yield 1.0+ g of (4) as an oil/low melting solid.

10 Step C: 12-(Isopropylthio)dodecanoic acid (6)

15 A mixture of 12-bromododecanoic acid (5) (0.558 g, 2.0 mM) and sodium isopropylthiolate (1.1 g, 11.2 mM) in 1,2-dimethoxyethane (50 mL) was deaerated (N<sub>2</sub>), heated to 85°C (bath temperature), and kept at this temperature for 72 hours. The cooled mixture was filtered, the collected solid dissolved in water and filtered. The stirred solution was acidified with dilute hydrochloric acid, aged, filtered, the solid washed well with water and dried. There was obtained product 6 (0.54 g) as a white solid.

When other halo-acids are used in place of 12-bromododecanoic acid in the above example, the corresponding (isopropylthio)-acid is obtained.

25 Likewise, when other mercaptan salts are used in place of sodium isopropylthiolate in the above example, the corresponding (alkylthio)alkanoic acids are obtained.

Representative of, but not limited to, the acids obtained by this procedure are:

30 8-(Isopropylthio)octanoic acid

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- 10-(Isopropylthio)decanoic acid  
10-(Ethylthio)decanoic acid  
11-(t-Butylthio)undecanoic acid  
14-(n-Propylthio)tetradecanoic acid  
5 9-(Methylthio)nonanoic acid

Step D: Ethyl 4-(2-(12-(Isopropylthio)dodecanoyl-  
amino)-phenoxy)-butyrate (7)

- 10 To a solution of (4) (0.25 g, 1.14 mM) and  
(6) (0.274 g, 1.0 mM) in dry methylene chloride (10  
mL) at room temperature was added 4-dimethylamino-  
pyridine (0.122 g, 1.0 mM) followed within one minute  
by a solution of N,N'-dicyclohexylcarbodiimide (0.22  
15 g, 1.06 mM) in methylene chloride (1 mL), 3X1 mL  
rinses with methylene chloride. After 2 days, the  
filtered mixture was concentrated in vacuo and the  
residue flash chromatographed on silica gel using  
15-20% ethyl acetate in hexane as eluant to give  
20 product 7 (0.22 g) as an oil that solidified readily  
in a short time.

Step E 4-(2-(12-(Isopropylthio)dodecanoylamino)  
phenoxy)-butyric acid (8)

- 25 A stirred solution of ester (7) (0.124 g,  
0.258 mM) in methanol (10 mL) was treated at room  
temperature under a nitrogen atmosphere with 2.5N  
sodium hydroxide solution (0.6 mL). Methanol (2X2  
mL) was used to clear the mixture, and the reaction  
30 allowed to continue until TLC analysis showed no  
ester remained. The filtered mixture was concen-

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trated in vacuo and the residue obtained stirred with water (30 mL). After aging, the mixture was filtered (The cake is the sodium salt of the product (100 mg), and the stirred filtrate acidified with dilute hydrochloric acid, aged, filtered, washed with water and dried to give product 8 (0.02 g) as a white solid. M.P. 82-84°C, with softening from 66°C.

Treatment of 8 with NaIO<sub>4</sub> as in Step J<sub>a</sub> will produce the corresponding sulfoxide, and treatment of 8 with m-chloroperbenzoic acid with Step J<sub>b</sub> will produce the corresponding sulfone.

Step F: 4-(2-(12-(Isopropylthio)dodecanoylamino)phenoxy)-butyramide (9)

To a stirred solution of (7) (20 mg, 0.041 mM) in methanol (10 mL) is added methanol saturated with ammonia (5 mL) and the stoppered mixture allowed to stir at ambient temperatures until TLC analysis shows little or no (D) remains. Concentration of the reaction mixture followed by preparative thin layer chromatography (silica gel; 3% methanol/methylene chloride as eluant) yields product 9 (11 mg) as a waxy solid.

Step G: Ethyl 4-(2-Amino-phenylthio)butyrate (11)

To a stirred deaerated (N<sub>2</sub>) solution of 2-aminothiophenol (10) (1.25 g., 10mM) and ethyl 4-bromobutyrate (2.14g., 11mM) in 40mL. of dry 1,2-dimethoxyethane is added 8.3g. of solid ground anhydrous potassium carbonate, the resultant mixture

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deaerated 3X under nitrogen and allowed to stir at room temperature until TLC analysis indicates the reaction is complete. The filtered mixture is then concentrated and the residue flash chromatographed on silica gel (85g.) using 15% ethyl acetate/hexane as eluant to give 1.8g. of (11) as a pale tan oil.

Step H: Ethyl 4-(2-(10-(Isopropylthio)decanoylamino)-phenylthio)butyrate (12)

When (11) and 10-(Isopropylthio)decanoic are reacted together analogously as per the conditions in Step (D) above, the title compound 12 is obtained.

Step I: 4-(2-(10-(Isopropylthio)decanoylamino)-phenylthio)-butyric acid (13)

When (12) is hydrolyzed as per the conditions of Step (E) the title compound 13 is obtained.

Step J: 4-(2-(11-(ethylsulfinyl)undecanoylamino)phenoxy)-butyric acid

When the subject esters or acids are treated with sodium metaperiodate (Step J<sub>a</sub>) in a suitable solvent (e.g. acetone/water) the corresponding sulfoxides are obtained. Treatment with meta-chloroperbenzoic acid (Step J<sub>b</sub>) yields the corresponding sulfones. For example, when ethyl 4-(2-(11-(ethylthio)undecanoylamino)phenoxy)-butyrate 14 (0.045 g, 0.1 mM) in acetone (10 mL) is reacted with sodium metaperiodate (0.072 g, 0.33 mM) in water (2 mL) at room temperature the corresponding

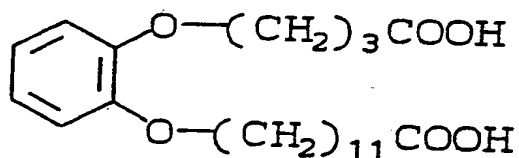
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side 15 is obtained. Hydrolysis as per Step (E) product 16 as an off-white solid. Finally, treatment of 14 with m-chloroperbenzoic acid will produce the sulfone 17, which yields the 8 upon hydrolysis using the hydrolysis conditions of Step E.

The method of preparing the novel compounds of the present invention, already described above in general terms, may be further illustrated by the following examples which should not be construed as limitations on the scope or spirit of the invention.

EXAMPLE 2

is of 4-(2-(11-Carboxyundecyloxy)phenoxy)-undecanoic acid (7)

7

1 4-(2-Benzoyloxyphenoxy)-butyrate (3)

To a stirred solution of 2-benzyloxyphenol (1.0 g, 20 mM) and ethyl 4-bromobutyrate (2) (1.87 mM) in dried acetone (100 mL) was added 1.0 g ground potassium carbonate (6.0 g, 44 mM). The resultant mixture heated at reflux under

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nitrogen until TLC analysis showed the absence of the starting phenol. Flash chromatography (silica gel, 15% ethyl acetate/hexane as eluant) of the filtered and concentrated mixture yielded 3.0 g of product (3) as a clear oil.

When the ethyl 4-bromobutyrate is replaced by halo-esters in the above example, the corresponding ether-ester is obtained. Likewise, when the above phenol is replaced by other substituted 2-benzyloxyphenols, the corresponding 2-substituted ethers are obtained. Substitution of a 2-benzyloxy- or a 2-benzylthio-thiophenol for the 2-benzyloxy-phenol yields the corresponding thioether-ester.

B. Ethyl 4-(2-Hydroxyphenoxy)-butyrate (4)

A mixture of (3) (1.57 g, 5.0 mM), ethanol (50 mL), glacial acetic acid (7 drops) and 10% palladium on carbon (0.7 g) was reacted in a hydrogen atmosphere (40 p.s.i.) at room temperature until hydrogen uptake ceased. Concentration of the filtered mixture yielded the product (4) as an oil.

C. Ethyl 4-(2-11-(Carbomethoxy)undecyloxyphenoxy)butyrate (6)

When (4) (0.224 g, 1.0 mM) and methyl 12-bromododecanoate (5) (0.32 g, 1.1 mM) were reacted with potassium carbonate in acetone as per Example (A), there was obtained product 6 (0.3 g) as a colorless oil.

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When methyl 12-bromododecanoate is replaced by other halo esters in the above example, the corresponding diester is obtained.

5 D. 4-(2-(11-Carboxyundecyloxy)phenoxy)butyric acid (7)

To a stirred solution of (6) (0.102 g, 0.23 mM) in methanol (4 mL) and water (3 drops) was added 2.5 N sodium hydroxide solution (0.55 mL, 1.37 mM) dropwise, and the resultant mixture cleared with additional methanol (2 mL). When TLC analysis (2% methanol in methylene chloride (10 mL) containing glacial acetic acid (4 drops) indicated no mono- or diester remained, the methanol was removed in vacuo, the residue stirred with water (10 mL), and the solution filtered and acidified with 2N hydrochloric acid. Filtration of the resultant precipitate followed by washing with water and drying yielded product 7 (88 mg) as a white solid; M.P. collapses at 95°C, all melted at 105°C (uncorr.; A. O. Spencer Hot Stage).

Calculated for  $C_{22}H_{34}O_6$ :

C. 66.98; H. 8.69.

Found: C. 67.32; H. 8.45.

25 Compounds (1)-(7) all had NMR and Mass Spectral data consistent with their assigned molecular formulas.

30

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4-(2-(11-Carboxyundecyloxy)  
phenylsulfinyl)butyric acid(7B)

When the subject thioethers, e.g., Compound  
7A in Flow Sheet C, as the ester or acid, are treated  
with sodium metaperiodate in a suitable solvent  
(e.g., acetone/water) the corresponding sulfoxides  
are obtained. Likewise, reaction of the subject  
thioethers with m-chloroperbenzoic acid yields the  
corresponding sulfones. For example, when 4-(2-  
(11-carboxyundecyloxy)phenylthio butyric acid 7A  
(0.41 g, 1.0 mM) in acetone (25 mM) is reacted  
with sodium metaperiodate (0.72 g, 3.3 mM) in  
water at room temperature, the title sulfoxide  
7B is obtained. When the same starting material  
in methylene chloride is reacted with excess  
m-chlorobenzoic acid, the corresponding sulfone  
is obtained.

Compounds (3)-(16) all had NMR and Mass Spectral data  
consistent with their assigned molecular structures.

EXAMPLE 3

Preparation of 4-(2-(11-carboxyundecanoylamino)-  
phenoxy)butyric acid

Step A: Ethyl 4-(2-nitrophenoxy)butyrate (3)

To a stirred solution of 2-nitrophenol  
(1) (1.4 g, 10 mM) and ethyl 4-bromobutyrate (2.1 g,  
1.57 mL, 11 mM) in 35 mL of dry acetone is added 2 g  
(14.5 mM) of anhydrous, ground potassium carbonate.  
The resultant colored mixture is then heated under a



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nitrogen atmosphere at gentle reflux until the color due to the phenol anion has dissipated and a yellow mixture remains. Concentration of the cooled and filtered mixture yields an oil which on flash chromatography (silica gel, ethyl acetate/hexane-  
5 or methylene chloride as eluant) yields 2.4 g (96% yield) of the title compound (3) as an oily liquid.

Step B: Ethyl 4-(2-aminophenoxy)butyrate (4)

10 A solution of (3) (1.27 g, 5.0 mM) in 15 mL ethyl acetate containing 200 mg of 5% palladium on carbon is reacted in a hydrogen atmosphere (40 psig.) at room temperature until hydrogen uptake ceases. The mixture is then filtered and concen-  
15 trated in vacuo to yield 1.0+ g of (4) as an oil/low melting solid.

Step C: Dodecanedioic acid, mono methyl ester (6)

Diethyl dodecanedioate (5) (34.4 g, 0.12 M)  
20 is reacted with barium hydroxide octahydrate (19.2 g, 0.06 M) in methanol (240 mL) as per the analogous procedure of Org. Syn., Coll. Vol. III, p. 635 to yield 24.8 g of (6) as a white solid.

25 Step D: Dodecanedioic acid, mono methyl ester mono acid chloride (7)

A mixture of mono acid (6) (10.0 g, 0.041 M) and thionyl chloride (12.1 mL, 0.166 M) is refluxed for 5 hours, the excess thionyl chloride removed  
30 in vacuo, and the residual acid chloride repeatedly dissolved in dry benzene and concentrated until no thionyl chloride remains to yield 10.8 g of the title compound (7) as a waxy solid.

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Step E: Ethyl 4-(2-(11-carbomethoxyundecanoylamino)-phenoxy)butyrate (8)

To a stirred, ice-cold solution of 0.89 g (4.0 mM) amine (4) and dried triethylamine (1.2 mL) in dry ether (40 mL) is added dropwise over ca. 4 minutes a solution of acid chloride (7) (1.04 g, 4.6 mM) in 20 mL of dry ether. The resultant mixture is allowed to stir cold for 20 minutes, and then at room temperature overnight. After filtering off the triethylamine hydrochloride, the ether filtrate is concentrated in vacuo and the residue chromatographed on an 82 g silica gel column using 20% ethyl acetate/hexane as eluant to give 1.49 g (85%) of (8) as a waxy solid.

The ether/triethylamine in the above reaction may be replaced by methylene chloride/pyridine with similar results. The same compound may also be prepared via direct coupling of acid (6) with the same amine using common coupling reagents, such as dicyclohexylcarbodiimide/N,N-dimethylamino-pyridine, and the like.

Step F: 4-(2-(11-Carboxyundecanoylamino)phenoxy)-butyric acid (9)

To a stirred solution of (8) (1.0 g, 2.22 mM) in methanol (100 mL) is added 1 mL of water followed by dropwise addition of 2.5 N sodium hydroxide solution (4.0 mL). The walls of the reaction flask are rinsed down with 10 mL of methanol and the mixture is stirred under a nitrogen atmosphere until TLC analysis shows no ester (mono- or di-) remaining. The methanol is removed in vacuo, the residue taken up in 100 mL

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of water, stirred for solution, filtered (20 mL water rinses), and the stirred filtrate acidified dropwise with 2 N hydrochloric acid. Filtration of the resultant precipitate followed by copious water washing and drying gave 0.87 g (96%) of (9) as a chalk-like white solid. The compound was one component by TLC (silica gel, the eluant was 10 mL of 2% methanol in methylene chloride containing 4 drops of glacial acetic acid). mp 128.5-130°C uncorr.

Microanalysis: Calc.: C, 64.84; H, 8.16; N, 3.44.  
Found: C, 64.90; H, 8.34; N, 3.33.

Step G: Ethyl 4-(2-Amino-3-methylphenylthio)  
butyrate (11)

To a stirred deaerated (N<sub>2</sub>) solution of 2-aminothiophenol (10) (1.25 g., 10 mM) and ethyl 4-bromobutyrate (2.14 g., 11 mM) in 40 mL. of dry 1,2-dimethoxyethane is added 8.3 g. of solid ground anhydrous potassium carbonate, the resultant mixture deaerated 3X under nitrogen and allowed to stir at room temperature until TLC analysis indicates the reaction is complete. The filtered mixture is then concentrated and the residue flash chromatographed on silica gel (85 g.) using 15% ethyl acetate/hexane as eluant to give 1.8g. of (11) as a pale tan oil.

Step H: 4-(2-(11-Carboxyundecanoylamino)  
phenylthio)butyric acid (13)

When amine (11) is acylated with acid chloride (7) as per procedure Step (E), and the resultant diester (ethyl 4-(2-(11-carbomethoxy-

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undecanoylamino)phenylthio)butyrate 12 is hydrolyzed in Step I as per procedure (F), the title compound, 13 m.p. 113.5-115°C is obtained.

The following representative compounds in this series were additionally made by the procedures outlined above:

- 14) 4-(2-(9-Carboxynonanoylamino)phenoxy)butyric acid, m.p. 121.5-124.5°C.
- 15) 4-(2-(10-Carboxydecanoylamino)phenoxy)butyric acid, m.p. 110-111.5°C.
- 16) 4-(2-(12-Carboxydodecanoylamino)phenoxy)butyric acid, m.p. 116-119°C.
- 17) 4-(2-(13-Carboxytridecanoylamino)phenoxy)butyric acid, m.p. 128-129.5°C.
- 18) 4-(2-(15-Carboxypentadecanoylamino)phenoxy)butyric acid, m.p. 121-125°C.
- 19) 5-(2-(11-Carboxyundecanoylamino)phenoxy)valeric acid, m.p. 112-113.5°C.
- 20) 4-(2-(11-Carboxyundecanoylamino)-3-methylphenoxy)butyric acid, m.p. 134.5-136.5°C.
- 21) 4-(2-(11-Carboxyundecanoylamino)-4-methylphenoxy)butyric acid, m.p. 99.5-100.5°C.
- 22) 4-(2-(11-Carboxyundecanoylamino)-5-methylphenoxy)butyric acid, m.p. 109.5-113°C.

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Step J: Benzyl 2-Nitrophenyl Ether (23)

When 2-nitrophenol (1) is reacted with benzylbromide under the conditions of Step A  
5 the title ether (23) is obtained as a golden oil.

Step K: Benzyl 2-Aminophenyl Ether (24)

A solution of benzyl 2-nitrophenyl ether  
10 (23) (1.15g., 5.0 mM) in ethanol (25 mL) saturated with anhydrous ammonia is stirred under a hydrogen atmosphere (40 p.s.i.) with Raney Nickel (2 g.) until TLC analysis indicates the absence of starting nitro  
15 compound. The filtered mixture is freed of excess ammonia by bubbling in anhydrous nitrogen. Removal of ethanol via vacuum distillation at room temperature yields 1.0 g. of title compound (24) as a deep colored crust, which was used as-is in the next  
20 reaction. This compound may also be obtained via careful reduction in ethanol or ethyl acetate using palladium on carbon as catalyst, but can be accompanied by slight over-reduction if not monitored.

Step L: N-Trifluoroacetyl 2-Benzyloxyaniline (25)

25 To a stirred, near solution of amine (24) (5.0 mM) in dry diethyl ether (30 mL) is added anhydrous sodium carbonate (6.0g., 57 mM) and the resultant mixture cooled in an ice-water bath. Trifluoroacetic anhydride (1.5 mL, 10.6 mM) is added  
30 dropwise to this cold mixture over 2 minutes, the color changing to a yellowish red. After 2 hours the cooling-bath is removed and the mixture allowed

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to stir at ambient temperatures overnight. After filtering, the filtrate is concentrated in vacuo and then pumped to yield 1.3 g. of the title compound (25) as a pale tan (with some reddish-brown color around the edges) crust.

Step M: N-Methyl-2-Benzyloxyaniline (27)

A well-stirred solution of (25) (0.295 g., 1.0 mM), methyl iodide (0.25 mL, 4.0 mM) and anhydrous acetone (5.0 ml) is set in an oil-bath previously heated to 59°C, and kept for 2 minutes. Powdered anhydrous potassium hydroxide (0.225g., 4.0 mM) is added all at once, and the bath temperature allowed to rise to 65°C. Clumping-up of some of the KOH is observed. After 15 additional minutes, the reaction mixture is removed from the bath, allowed to cool, and the volatiles removed. Methanol (7 mL) is added with stirring to the residue of N-Methyl-N-trifluoroacetyl-2-benzyloxyaniline (26) obtained, followed by water (1 mL), and methanol (2 mL) (to wash down the sides). After stirring overnight at ambient temperatures, the methanol is removed in vacuo, the residue distributed between ether and water, separated, the organic layer washed with additional water, saturated sodium chloride solution, and dried over sodium sulfate. Concentration of the filtered ether solution gives the title compound (27) (0.212 g.) as an oil. NMR, MS, and TLC indicate little, if any, dimethyl compound.

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Step N: N-(11-(Carbomethoxy)undecanoyl)-  
N-Methyl-2-Benzoyloxyaniline (28)

To a stirred ice-cold solution of (27)  
(0.21 g., 1.0 mM) in dried methylene chloride  
5 (10 mL) containing anhydrous pyridine (0.3 mL)  
is added (7) (0.27 g., 1.03 mM), dissolved in 5  
methylene chloride (5 mL), dropwise over 1 minute  
(some methylene chloride used as a rinse). After  
stirring cold for 30 minutes, the mixture is allowed  
10 to stir at ambient temperature for completion of the  
reaction. The reaction mixture is washed 1X with  
1N HCL, dried (Na<sub>2</sub>SO<sub>4</sub>) and filtered. Flash chroma-  
tography (silica gel, 20% ethyl acetate/hexane as  
eluant) of the residue obtained gives the title  
15 compound (28) (0.33 g) as a colorless oil.

Step O: N-(11-(Carbomethoxy)undecanoyl)-  
N-Methyl-2-Hydroxy aniline (29)

A solution of (28) (0.11 g., 0.25 mM) in  
20 methanol (11 mL) containing 10% palladium on carbon  
(30 mg.) is shaken in a 40 p.s.i. hydrogen atmosphere  
until no (V) remained (TLC analysis). The filtered  
solution was then concentrated in vacuo to give the  
title compound (29), used immediately in step P.

25

Step P: Ethyl 4-(2-N-(11-Carbomethoxyundecanoyl)-  
N-(methyl)-amino)phenoxybutyrate (30)

To a stirred solution of (29) (0.087 g.,  
0.25 mM) and ethyl 4-bromobutyrate (0.115 mL, 0.80  
30 mM) in anhydrous acetone (10 mL) is added anhydrous  
ground potassium carbonate (0.45 g., 3.2 mM) and the

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resultant mixture heated under gentle reflux under a nitrogen atmosphere for 24 hours. The mixture is cooled, filtered, and concentrated, and the residue flash chromatographed (silica gel; 20% ethyl acetate/hexane eluant) to give 80 mg. of the title compound (30) as a colorless oil.

Step Q: 4-(2-N-(11-Carboxyundecanoyl)-N-(methyl)-amino)-phenoxybutyric Acid (31)

When (30) (0.055 g., 0.118 mM) is hydrolyzed as per its N-desmethyl analog (Step F, supra), and the resultant oil obtained after acidification is extracted with methylene chloride, there is obtained the title compound (31), (51 mg.), as a colorless oil.

Step R: Ethyl 4-(2-(11-Bromoundecanoylamino)phenoxy)-butyrate (32)

To a solution of (4) (2.60 g., 11 mM) and 11-bromoundecanoic acid (2.65 g., 10 mM) in anhydrous methylene chloride (90 mL) is added 4-(dimethylamino)pyridine (1.22 g., 10 mM) followed by N,N'-dicyclohexylcarbodiimide (2.3 g., 11 mM) (4X5 mL of methylenechloride rinses). Precipitation of dicyclohexylurea (DCU) begins within 4 minutes. When TLC analysis indicates the reaction is complete, the mixture is filtered, the filtrate concentrated in vacuo and the residue extracted with ether. The combined ether extracts are washed 1X with 1N hydrochloric acid, 1X saturated sodium chloride solution, dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to a residue which is stirred, filtered, and concentrated alternately with ether and methylene chloride until all DCU is removed.



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Concentration of the final solution yields the title product (32) (2.35 g.) as an oil that goes readily to a waxy solid.

5 Attempted purification of an earlier run via column chromatography (silica gel; 20% ethyl acetate/hexane as eluant) gave an impure product of greatly diminished yield.

10 Step S: Diethyl 10-(N-((2-(3-Carboethoxy)propyloxy)-phenyl)carboxamido)decylphosphonate (33)

A stirred mixture of (32) (0.235 g., 0.5 mM) and triethyl phosphite (TEP) (0.3 mL) is heated at 180°C (bath temperature) under a nitrogen atmosphere for 8 hours, cooled, excess TEP removed in vacuo, and the residue flash chromatographed (Silica gel; ethyl acetate as eluant) to yield product 33 (0.13 g.) as a clear colorless oil.

20 Step T: Cleavage of the phosphonate ester (33) using bromotrimethylsilane (procedure of J.C.S. Chem. Comm. p.739 (1979) yields 10-(N-((2-(3-(Carboethoxy)-propyloxy)phenyl)carboxamido)decylphosphonic acid (34).

25 Step U: Further hydrolysis of (34) using the procedure of Example (F) above yields the corresponding di-acid, 10-(N-((2-(3-Carboxy)propyloxy)phenyl)carboxamido)-decylphosphonic acid (35).

30

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Step V: 10-(N-((2-(3-Carboethoxy)propyloxy)phenyl)-carboxamido)decanethiouronium bromide (36)

5 A stirred solution of (32) (0.047 g., 0.1 mM) in ethanol (2 mL) is reacted with thiourea (0.010 g., 0.13 mM) under the same conditions as (in Step W.). Concentration of the reaction mixture yields the title compound (36) (contaminated with a small amount of thiourea) which slowly solidifies in crystalline circles on standing. Stirring with dried chloroform followed by filtration and concentration yields the product as a thick wax.

Step W: Sodium 10-(N-((2-(3-Carboethoxy)propyloxy)-phenyl)carboxamido)decanethiosulfate (37)

15 To a stirred solution of (32) (0.047 g., 0.1 mM) in ethanol (2.0 mL) is added water (10 drops, slowly) followed by sodium thiosulfate (0.035 g., 0.14 mM), and the reaction mixture heated in an oil-bath (bath temperature ca. 90°C) under a nitrogen atmosphere until TLC analysis indicated no starting bromo compound. The cooled mixture was then concentrated to remove the ethanol and water yielding a white crust. Extraction of this crust with chloroform, followed by filtration from inorganics, yielded product (37) (49 mg.) as a glaze which goes with time to a waxy solid. This product has appreciable water solubility.

30

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Oxidation of (36) or (37) as per the analogous procedures in J.S. Showell et al., J. Org. Chem 27 (1962) 2853 or C. Ziegler et al J. Org. Chem. (1951) 621) yields the corresponding sulfonic acid (38).

Step X: Ethyl 4-(2-Nitropyrid-3-yloxy)butyrate (40)

This compound was prepared from ethyl 4-bromobutyrate 2 and 2-nitro-3-pyridinol (39) via the procedure of Step (A), supra. Following flash chromatography (silica gel; 1.5% methanol/methylene chloride eluant) a dilute sodium bicarbonate wash of an ether solution of the product was necessary to remove traces of starting phenol. The product (40) was obtained in 76% yield as a pale yellow oil.

Step Y: Ethyl 4-(2-Aminopyrid-3-yloxy)butyrate (41)

This compound was prepared via reduction of (40) as per the procedure of step (B), above. The amine (41) was obtained as a waxy solid.

Step Z: Ethyl 4-(2-(11-Carbomethoxyundecanoylamino)pyrid-3-yloxy)butyrate (42)

When (41) and (7) are reacted as per the procedure of step (E), above, the title compound (42) is obtained. Hydrolysis will yield the corresponding di-acid (4-(2-(11-Carboxyundecanoylamino)pyrid-3-yloxy)butyric acid (43).

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Step AA: N-(11-Carbomethoxyundecanoyl)-2-hydroxyaniline (44)

To a stirred near solution of 2-aminophenol (0.24 g, 2.2 mM) in anhydrous methylene chloride (25 mL) was added dry pyridine (0.66 mL) and the mixture cooled in an ice-water bath. A solution of (7) (0.525 g, 2.0 mM) in methylene chloride (2 mL) was added over 1 minute (2X1.5 mL methylene chloride rinses), and the mixture allowed to stir cold. After 30 minutes the bath was removed. After stirring overnight at ambient temperatures, the mixture was filtered, the solvents removed in vacuo, and the residue pumped to remove all traces of pyridine. The product, (44) was used as is in subsequent steps.

Step BB: 4-(2-(11-Carbomethoxyundecanoylamino)phenoxy)-butyronitrile (45)

When (44) and 4-bromobutyronitrile are reacted under the conditions of step (A), above, (45) is obtained as a waxy solid. Conversely, reacting (44) with ethyl 4-bromobutyrate as in step (A) yields (8).

Step CC: 4-(2-(11-Carbomethoxyundecanoylamino)phenoxy)-butyramide (46)

To a stirred solution of (45) (11 mg, 0.027 mM) in methylene chloride (3 mL) is added activated manganese dioxide (100 mg) and the resultant suspension allowed to stir stoppered at room temperature. After a few days some additional methylene chloride and manganese dioxide (100 mg) are added and the

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reaction allowed to continue. This is repeated one additional time. When TLC analysis shows no nitrile remains the mixture is filtered, the catalyst washed well with fresh methylene chloride, and the filtrate concentrated to yield the title product, (46) as a waxy solid.

The above new isolated, purified compounds had NMR and Mass spectra consistent with their assigned chemical structures. All melting points were taken on an A.O. Spencer hot stage and are uncorrected.

#### CHAPTER 4

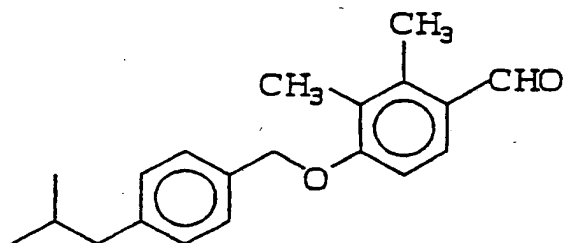
#### EXAMPLE 1

#### 17B-Benzoyl-Androst-3,5-diene-3-Carboxylic Acid

The title compound is made by reacting 17B-carbomethoxy-androst-3,5-diene-3-protected carboxylic acid in e.g., THF, with phenyl magnesium bromide under standard Grignard conditions. Standard workup procedure yields the title compound, m.p.222-225°C.

#### REFERENCE EXAMPLE 1

#### Synthesis of 4-(4-isobutylbenzyloxy)-2,3-dimethyl-benzaldehyde



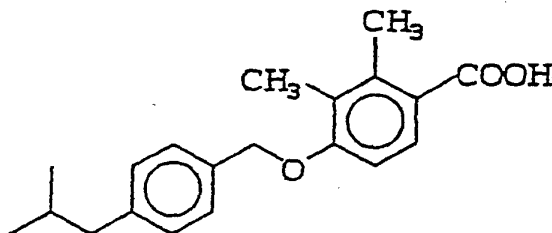
- 256 -

A mixture of 4-hydroxy-2,3-dimethyl-benzaldehyde (220 mg), 4-isobutylbenzyl bromide (341 mg), potassium carbonate (1.38 g) and ethyl methyl ketone (10 ml) was refluxed for 6 hrs. After cooling, the reaction mixture was diluted with ethyl acetate, the solution was washed with dil hydrochloric acid, water, successively, dried and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 10:1) to give the title compound (383 mg) having the following physical data:

TLC: Rf 0.48 (hexane:EtOAc=5:1); NMR:  $\delta$  7.64 (1H, d), 7.32 (1H, d), 7.16 (1H, d), 5.12 (2H, s), 2.60 (3H, s), 2.48 (2H, d), 2.24 (3H, s), 1.94-1.80 (1H, m), 0.90 (6H, d).

#### REFERENCE EXAMPLE 2

Synthesis of 4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoic acid

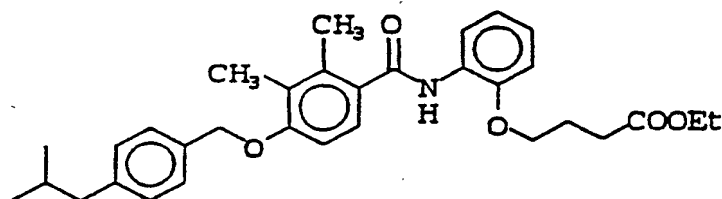


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A solution of the aldehyde prepared in reference example 1 (380 mg) in acetone (5 ml) was cooled with ice. To the solution, Jones' reagent (2.67 N; 2 ml) was dropped and allowed to stand. The solution was stirred for 1.5 hrs at room temperature. The reaction was stopped by addition of isopropyl alcohol. The crystals deposited were washed with hexane, dried and purified by column chromatography on silica gel (hexane-EtOAc) to give the title compound (328 mg) having the following physical data: TLC: Rf 0.36 (hexane:EtOAc=2:1); NMR:  $\delta$  7.80 (1H, d), 7.33 (1H, d), 7.15 (1H, d), 6.90 (1H, d), 5.09 (2H, s), 2.58 (3H, s), 2.48 (2H, d), 2.26 (3H, s), 0.91 (6H, d).

### REFERENCE EXAMPLE 3

Synthesis of 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzovlamino]phenoxy]butanoic acid ethyl ester



Oxalyl chloride (2 ml) was dropped to a solution of the carboxylic acid prepared in reference example 2 (325 mg) in methylene chloride (2 ml). The solution was stirred for 1 hr and evaporated. To an ice-cooled mixture of ethyl 4-(2-aminophenoxy)-butanoate (232 mg), pyridine (1 ml) and methylene chloride (15 ml), the above solution was dropped.

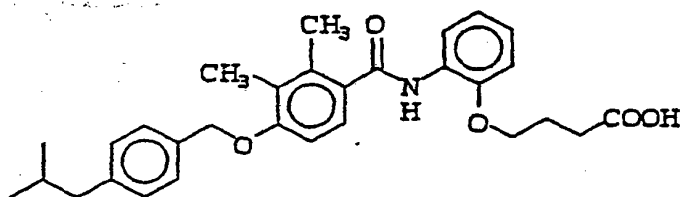
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The mixture was stirred for 30 mins at the same temperature and for 1 hr at room temperature. The reaction solution was washed with water, dried and evaporated. The residue was purified by column chromatography on silica gel (hexane:EtOAc = 5:1) to give the title compound (383 mg) having the following physical data:

TLC: Rf 0.5 (hexane:EtOAc=3:1); NMR:  $\delta$  8.58-8.48 (1H, m), 8.05 (1H, s), 7.34 (H, d), 7.16 (1H, d), 7.08-6.96 (2H, m), 6.90-6.80 (2H, m), 5.07 (2H, s), 4.14-3.96 (4H, m), 2.49 (2H, d), 2.44 (3H, s), 1.18 (3H, t), 0.91 (6H, d).

#### REFERENCE EXAMPLE 4

Synthesis of 4-[2-[4-(4-isobutylbenzyloxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid



1N aq. Solution of lithium hydroxide (3 ml) was added to a solution of the ester prepared in Reference Example 3 (380 mg) in dimethoxyethane (8 ml). The mixture was stirred for 30 mins at 50°C. After reaction, the solution was neutralized with dil. hydrochloric acid and was extracted with ethyl acetate. The extract was dried and evaporated. The



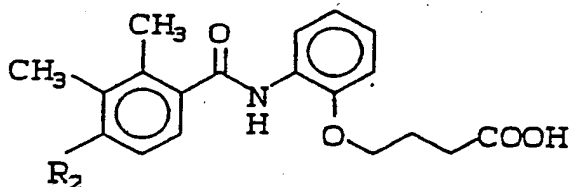
- 259 -

residue obtained was recrystallized from hexane to give the title compound (317 mg) having the following physical data:

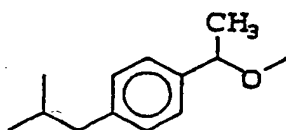
TLC: Rf 0.26 (hexane:EtOAc = 1:1): mp: 143°C.

REFERENCE EXAMPLE 5

By the similar procedure as reference examples 1, 2, 3 and 4, the following compound was made, 4-[2-[4-[1-(4-isobutylphenyl)-ethoxy)-2,3-dimethylbenzoylamino]phenoxy]butanoic acid, having the structural formula:



where R<sub>2</sub> is



in which the Rf value is 0.37 (hexane:EtOAc = 1:1), and the mass spectrum exhibited m/z values of 503, 345.

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REFERENCE EXAMPLE 6

(-)-4-[2-(4-[1-(4-isobutylphenyl)ethoxy]-2,3-dimethyl-  
benzoylamino phenoxy]butanoic acid

5       The compound prepared above in reference  
example 5, (403 mg) and cinchonidine (2.36 g) were  
dissolved into acetone (70 ml) with heating. The  
solution was allowed to stand to give white  
crystals. The crystals were gathered by filtration  
10       and purified by recrystallization from acetone four  
times. The white crystals obtained were dissolved  
into chloroform. The solution was washed with dil.  
hydrochloric acid. The oily layer was washed with  
water, dried and evaporated to give the title  
15       compound having the following physical data:  
Appearance: white crystal;  
Optical angle of rotation:  $[\alpha]_D -39.6^\circ$  (c=1,  $\text{CHCl}_3$ )

REFERENCE EXAMPLE 7

20       Sodium salt of (-)-4-[2-(4-[1-(4-isobutylphenyl)-  
ethoxy]-2,3-dimethylbenzoylamino)phenoxy]butanoic acid

25       The compound prepared in Reference Example 6  
was dissolved into methanol. The equivalent molar of  
an aq. Sodium hydroxide solution was added and  
evaporated to give the title compound having the  
following data:  
IR:  $\nu$  3050, 1750, 1580, 1560, 1510, 1445, 1260, 1090,  
1020, 740  $\text{cm}^{-1}$ .

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FORMULATION EXAMPLE

The following components are admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

5

4-[2-[4-[1-(4-isobutylphenyl)ethoxy)- 5 g

2,3-dimethylbenzoylamino)phenoxy]

butanoic acid

Cellulose calcium gluconate 0.2 g

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(disintegrating agent)

Magnesium stearate 0.1 g

(lubricating agent)

Microcrystalline cellulose 4.7 g

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20

25

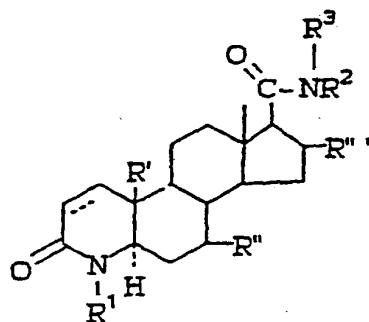
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WHAT IS CLAIMED IS:

1. A method of treating benign prostatic hyperplasia in patients who are in need of such treatment comprising the step of administering to such patients therapeutically effective amounts of a 5 $\alpha$ -reductase inhibitor selected from 17 $\beta$ -substituted non azasteroids, 17 $\beta$ -acyl-3-carboxyandrost-3,5-dienes, benzoylaminophenoxy butanoic acid derivatives, cinnamoylamides, fused benz(thio)amides, aromatic 1,2-diethers or thioethers, aromatic orthoacylaminophenoxy alkanolic acids, orthothioalkylacylaminophenoxyalkanoic acids, or pharmaceutically acceptable ester or salts thereof in combination with an aromatase inhibitor.

2. The method of Claim 1 wherein said 5 $\alpha$ -reductase inhibitor is  
(a) a 17 $\beta$ -substituted 4-aza steroid of the formula:



wherein:

the dotted line represents a double bond when present;  
R¹ and R³ are independently hydrogen, methyl or ethyl;  
R² is a hydrocarbon radical, selected from substituted or unsubstituted straight or

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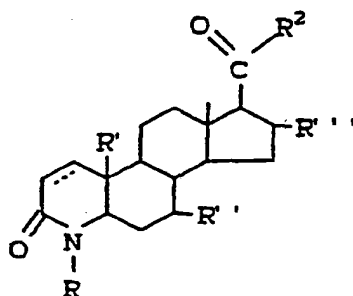
branched chain alkyl, cycloalkyl, or aralkyl of from 1-12 carbons or monocyclic aryl optionally containing 1 or more lower alkyl substituents of from 1-2 carbon atoms and/or 1 or more halogen substituents;

R' is hydrogen or methyl;

R'' is hydrogen or  $\beta$ -methyl;

R''' is hydrogen,  $\alpha$ -methyl or  $\beta$ -methyl, and pharmaceutically acceptable salts or esters thereof;

(b) a 4-aza steroid of the formula:



wherein the dotted line represents a double bond when present and ,

R is selected from hydrogen, methyl and ethyl; and

R<sup>2</sup> is (a) a monovalent radical selected from straight or branched chain alkyl, or cycloalkyl, of from 1-12 carbons, which can be substituted by one or more of C<sub>1</sub>-C<sub>2</sub> alkyl or halo;

(b) an aralkyl radical selected from benzyl or phenethyl;

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(c) a polycyclic aromatic radical which can be substituted with one or more of:

-OH, protected -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, halo or nitro;

(d) a monocyclic aromatic radical which can be substituted with one or more of:

(1) -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>, COOH, including protected hydroxy, where m is 1-4, n is 1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present when one of the above oxygen-containing radicals is present;

(2) -SH, -SC<sub>1</sub>-C<sub>4</sub> alkyl, -SOC<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>C<sub>1</sub>-C<sub>4</sub> alkyl, -SO<sub>2</sub>N(C<sub>1</sub>-C<sub>4</sub>-alkyl)<sub>2</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl -(CH<sub>2</sub>)<sub>m</sub>SH, -S-(CH<sub>2</sub>)<sub>n</sub>-O-COCH<sub>3</sub>, where m is 1-4 n is 1-3, providing C<sub>1</sub>-C<sub>4</sub> alkyl is only present when one of the above sulfur containing radicals is present;

(3) N(R<sup>3</sup>)<sub>2</sub>, which can be protected, where R<sup>3</sup> is independently H or C<sub>1</sub>-C<sub>4</sub> alkyl, where the monoaryl ring can also be further substituted with C<sub>1</sub>-C<sub>4</sub> alkyl; and

(e) heterocyclic radical selected from 2- or 4-pyridyl, 2-pyrrolyl, 2-furyl or thiophenyl;

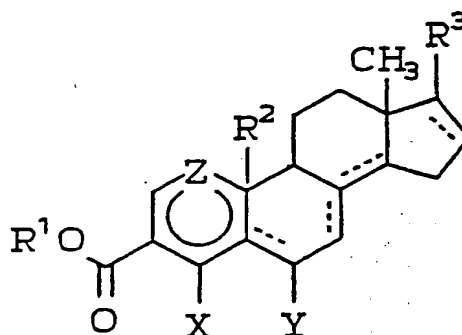
- 265 -

R', R'', R''' are each selected from hydrogen and methyl, and pharmaceutically acceptable salts thereof;

(c) a 17-substituted non-aza steroid of the formula:

5

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in which:

the A ring has up to 2 double bonds;

the B, C, and D rings have optimal double bonds where indicated by the broken lines,

20

provided that the A, B, and C rings do not have adjacent double bonds and the D ring does not have a C<sub>16</sub>-C<sub>17</sub> double bond when R<sub>3</sub> represents two substituents or a divalent substituent;

25

Z is (CH<sub>2</sub>)<sub>n</sub> and n is 0 or 2, provided that Z is (CH)<sub>n</sub> when adjacent to a double bond;

X is H, Cl, F, Br, I, CF<sub>3</sub>, or C<sub>1-6</sub> alkyl;

Y is H, CF<sub>3</sub>, F, Cl, or CH<sub>3</sub>, provided that Y is H when there is no C<sub>5</sub>-C<sub>6</sub> double bond;

R<sup>1</sup> is H or C<sub>1-8</sub> alkyl;

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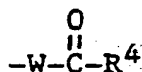
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$R^2$  is absent or present as H or  $CH_3$ , provided  $R^2$  is absent when the carbon to which it is attached is unsaturated; and

$R^3$  is

- 5 (1)  $\alpha$ -hydrogen, or  $\alpha$ -hydroxyl, or  $\alpha$ -acetoxy and/or

(a)



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where W is a bond or  $C_{1-12}$  alkylidene, and

$R^4$  is

- (i) hydrogen,
- (ii) hydroxyl,
- 15 (iii)  $C_{1-8}$  alkyl,
- (iv) hydroxylic  $C_{1-8}$  alkyl,
- (v)  $C_{1-8}$  alkoxy,
- (vi)  $NR^5R^6$ , where  $R^5$  and  $R^6$  are each independently selected from
- 20 hydrogen,  $C_{1-8}$  alkyl,  $C_{3-6}$  cycloalkyl, phenyl; or  $R^5$  and  $R^6$  taken together with the nitrogen to which they are attached represent a 5-6 membered saturated
- 25 ring,
- (vii)  $OR^7$ , where  $R^7$  is hydrogen, alkali metal,  $C_{1-8}$  alkyl, benzyl, or
- (b)  $-Alk-OR^8$ , where Alk is  $C_{1-12}$  alkylidene, and  $R^8$  is
- 30 (i) phenyl  $C_{1-6}$  alkylcarbonyl,
- (ii)  $C_{5-10}$  cycloalkylcarbonyl,
- (iii) benzoyl,

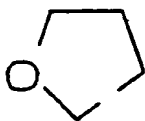


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- (iv) C<sub>1-8</sub> alkoxycarbonyl,
- (v) aminocarbonyl, or C<sub>1-8</sub> alkyl substituted aminocarbonyl,
- (vi) hydrogen, or
- (vii) C<sub>1-8</sub> alkyl,

(2) =CH-W-CO-R<sup>4</sup> or =CH-W-OR<sup>8</sup>, where W is a bond of C<sub>1-12</sub> alkylidene and R<sup>4</sup> and R<sup>8</sup> have the same meaning as above and R<sup>8</sup> also is hydrogen or C<sub>1-20</sub> alkylcarbonyl,

(3)



where the dashed bond replaces the 17- $\alpha$ -hydrogen,

(4)  $\alpha$ -hydrogen and NHCOR<sup>9</sup> where R<sup>9</sup> is C<sub>1-12</sub> alkyl or NR<sup>5</sup>R<sup>6</sup> where R<sup>5</sup> and R<sup>6</sup> have the same meaning as above,

- (5)  $\alpha$ -hydrogen and cyano,
- (6)  $\alpha$ -hydrogen and tetrazolyl, or
- (7) keto;

or a pharmaceutically acceptable salt thereof; except compounds in which:

- (i) the B ring has a C<sub>5</sub>-C<sub>6</sub> double bond, R<sup>1</sup> is CH<sub>3</sub>, and R<sup>3</sup> is keto, methoxycarbonyl, or acetyl; or
  - (ii) the A-nor ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>3</sup> is acetoxy or acetyl;
  - (iii) R<sup>1</sup> is CH<sub>3</sub> and R<sup>3</sup> is acetoxy or acetyl;
- or

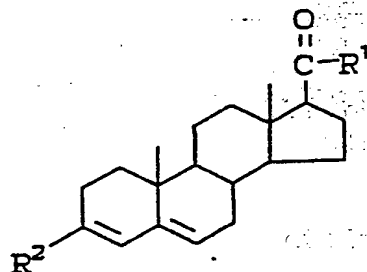
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- (iv) the A-nor ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>1</sup> is methyl; or  
(v) the B ring has a C<sub>3</sub>-C<sub>4</sub> double bond and R<sup>3</sup> is B-hydroxy;

5

(d) a 17B- acyl 3-carboxy-androst-3,5-diene of the formula:

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- wherein R<sup>1</sup> is (a) C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl; C<sub>3</sub>-C<sub>12</sub> cycloalkyl, which can be substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy or C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl; C<sub>6</sub>-C<sub>12</sub> aryl, or C<sub>7</sub>-C<sub>13</sub> aralkyl which can be substituted with one or more of: -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl, C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>COOH, including protected -OH, where m is 1-4, n is 1-3;
- (b) C<sub>1</sub>-C<sub>6</sub> linear or branched alkyl; C<sub>3</sub>-C<sub>12</sub> cycloalkyl, which can be substituted with C<sub>1</sub>-C<sub>4</sub> alkoxy

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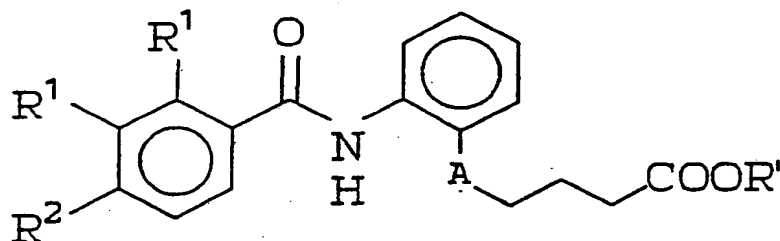
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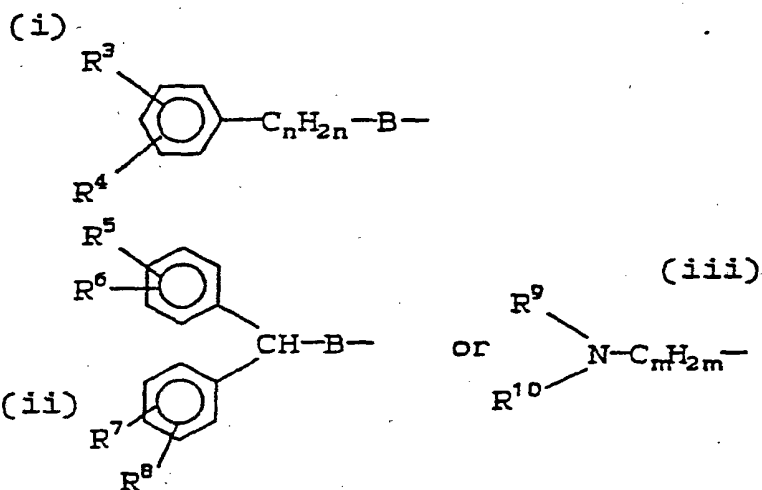
or C<sub>1</sub>-C<sub>4</sub> linear/branched alkyl;  
 C<sub>6</sub>-C<sub>12</sub> aryl, or C<sub>7</sub>-C<sub>13</sub> aralkyl  
 which can be substituted with one  
 or more of: -OH, -OC<sub>1</sub>-C<sub>4</sub> alkyl,  
 C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>m</sub>OH, -(CH<sub>2</sub>)<sub>n</sub>  
 COOH, including protected -OH,  
 where m is 1-4, n is 1-3, and  
 R<sup>2</sup> is selected from COOH, SO<sub>3</sub>H,  
 PO(OH)<sub>2</sub>, PH(O)OH;

(e) a benzoylaminophenoxy butanoic acid derivative of  
 the formula:



wherein R' is hydrogen or alkyl of from 1 to 4 carbon  
 atom(s); A is oxygen atom, sulfur atom or sulfinyl  
 (SO) group; both R<sup>1</sup>'s are methyl or chlorine, or the  
 two R<sup>1</sup>'s and the carbon atoms of the benzene ring to  
 which the two R<sup>1</sup>'s are linked together are  
 cyclopentane, cyclohexane or a benzene ring; and  
 R<sup>2</sup> represents a group of formula:

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15 wherein B is oxygen, sulfur or a group of formula:  
 $\text{NR}^{11}$  wherein  $\text{R}^{11}$  is hydrogen or alkyl of from 1 to 4  
 carbon atom(s),

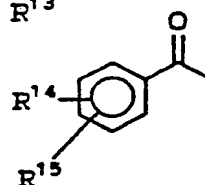
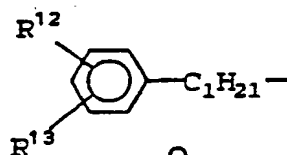
20  $\text{R}^3$ ,  $\text{R}^4$ ,  $\text{R}^5$ ,  $\text{R}^6$ ,  $\text{R}^7$ , and  $\text{R}^8$  are, independently,  
 hydrogen, alkyl of from 1 to 4 carbon  
 atom(s), halogen, trifluoromethyl or  
 cyclobutylmethyl,

$m$  is 0 or 1,

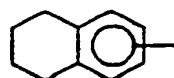
$n$  is an integer of from 1 to 5, and

25  $\text{R}^9$  is a hydrogen, alkyl of from 1 to 5 carbon  
 atom(s) or a group of formula:

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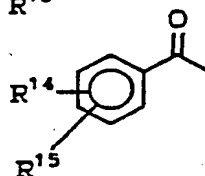
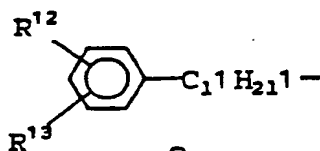


or

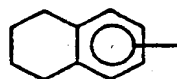


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wherein R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, and R<sup>15</sup> are,  
independently, hydrogen, alkyl of from 1 to  
4 carbon atom(s), halogen, trifluoromethyl  
or cyclobutylmethyl, and 1 is an integer of  
from 1 to 4, and  
R<sup>10</sup> is a group of formula:



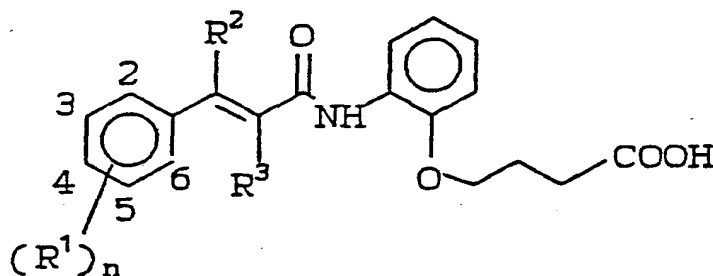
or



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wherein  $R^{12}$ ,  $R^{13}$ ,  $R^{14}$ , and  $R^{15}$  are,  
independently, hydrogen, alkyl of from 1 to 4  
carbon atom(s), halogen, trifluoromethyl or  
cyclobutylmethyl, and  $1'$  is an integer of from 1  
to 4; or non-toxic salts thereof;

(f) a cinnamoylamide of the formula:



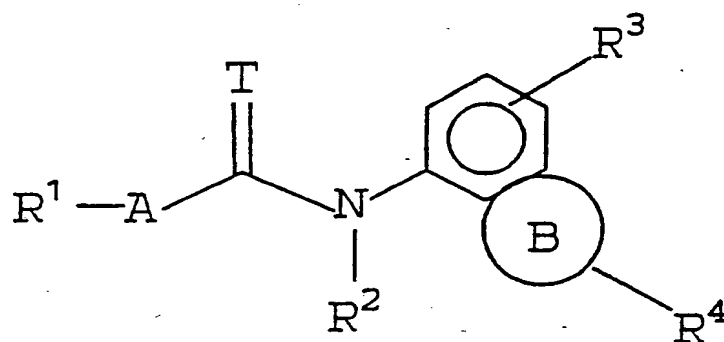
wherein  $R^2$  and  $R^3$  each independently represents a  
hydrogen or methyl group with the proviso that

- (i) when  $R^2$  represents a methyl group,  $R^3$   
represents hydrogen and  $(R^1)_n$  represents a  
member selected from the group consisting of  
3-group, 4-pentyl group, 4-neopentyl group,  
4-(2-ethylbutyl) group and  
4-(2-methylpentyl) group, or

- (ii) when  $R^2$  represents hydrogen,  $R^3$  represents a  
methyl group and  $(R^1)_n$  represents a 3-pentyl  
group, or non-toxic salts thereof;

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(g) a fused benz(thio)amide of the formula:



wherein A represents a single bond or a group of methylene, ethylene, trimethylene, tetramethylene, vinylene, propenylene, butenylene, butadienylene or ethynylene group optionally being substituted by one, two or three of straight or branched alkyl group(s) of from 1 to 10 carbon atom(s) and/or phenyl group(s);

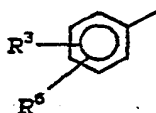
B represents a heterocyclic ring of from 4 to 8 members containing one, two or three hetero atom(s) selected from the group consisting of oxygen, nitrogen and sulphur atom(s), wherein the said ring may optionally be substituted by group(s) selected from oxo, thioxo and/or hydroxy group(s) including a ring of formula:

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T represents an oxygen atom or a sulphur atom;  
R<sup>1</sup> represents a group of general formula:

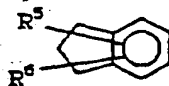
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(i)



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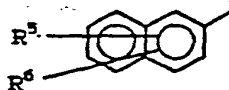
(iii)



or

(ii)

15



(iv) a straight or branched alkyl, alkenyl or  
alkynyl group of from 1 to 20 carbon  
atom(s), wherein R<sup>5</sup> and R<sup>6</sup> independently  
represent a hydrogen atom or a halogen atom  
or a straight or branched alkyl, alkenyl or  
alkynyl group of from 1 to 20 carbon atom(s)  
being unreplaced or replaced by one, two,  
three, four or five optional carbon atom(s),  
by oxygen atom(s), sulphur atom(s), halogen  
atom(s), nitrogen atom(s), benzene ring(s),  
thiophene ring(s), naphthalene ring(s),  
carbocyclic ring(s) of from 4 to 7 carbon  
atom(s), carbonyl group(s), carbonyloxy  
group(s), hydroxy group(s), carboxy group(s),  
azido group(s) and/or nitro group(s);

30

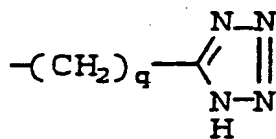
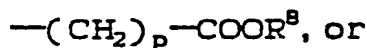
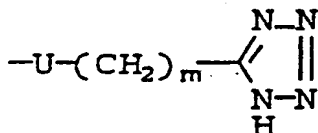
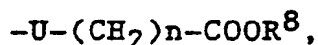


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$R^2$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s);

$R^3$  represents a hydrogen atom, a halogen atom, a hydroxy group, a nitro group, a group of general formula:  $--COOR^7$ , wherein  $R^7$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), or a straight or branched alkyl, alkoxy or alkylthio group of from 1 to 6 carbon atom(s);

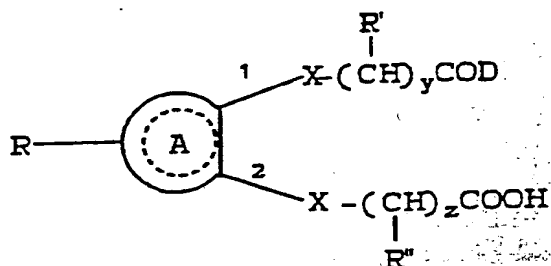
$R^4$  represents a group of general formula:



wherein U represents an oxygen atom or a sulphur atom,  $R^8$  represents a hydrogen atom or a straight or branched alkyl group of from 1 to 6 carbon atom(s), n and m represent an integer of from 1 to 10, respectively, p and q represent zero or an integer of from 1 to 10, respectively, or non-toxic salts thereof;

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(h) an ortho-acylamino-phenoxy alkanic acid of the structure:



wherein

A is an 1,2-disubstituted aromatic ring selected from

(a) benzene;

(b) 5-6 membered heteroaromatic ring, containing 1-2 N atoms, 1 S or 0 atom, or combination thereof;

D and E are independently  $-\text{COOH}$ ,  $-\text{CONH}_2$ ,  $-\text{CONHR}_b$ ,  $\text{SO}_2\text{OH}$ ,  $-\text{SO}_2\text{NH}_2$ ,  $-\text{CO}_2\text{R}_b$ ,  $-\text{SSO}_2\text{ONa}$ ,  $\text{SO}_3\text{OH}$ ,  $\text{P}(\text{O})(\text{OH})_2$ ;

X is O, S, SO or  $\text{SO}_2$ ;

R is H,

$\text{C}_1\text{-C}_4$  alkyl,

phenyl or substituted phenyl,

halo,

haloalkyl,

hydroxy,

carboxy,

cyano,

$\text{C}_1\text{-C}_4$  alkoxy,

$\text{C}_1\text{-C}_4$  alkylthio,

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C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl,

amino,

nitro,

5 C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;

R' and R'' are independently

H,

halo,

C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,10 amino, or oxo, where CH-R' or CH-R''  
in the formula become -C=O;R<sub>a</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl;15 R<sub>b</sub> is C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl, or phenyl C<sub>1</sub>-C<sub>4</sub> alkyl;

y is 1-6;

z is 6-20; and

20 wherein

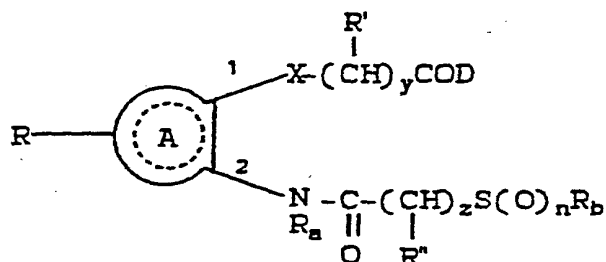
$$\begin{array}{c} \text{R}' \\ | \\ (\text{CH})_y \end{array} \text{ and}$$
25 
$$\begin{array}{c} \text{R}'' \\ | \\ (\text{CH})_z \end{array} \text{ can independently represent substituted}$$

or

30 unsubstituted alkyl or alkenyl radicals  
containing at least one alkene bond;  
and pharmaceutically acceptable salts and esters  
thereof;

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(i) an ortho-thioalkylacylaminophenoxy alkanoic acid  
of the structure:



wherein

A is a 1,2-disubstituted aromatic ring;

D is OH, NH<sub>2</sub>, NHR<sub>C</sub>, OR<sub>C</sub>;

X is O, S, SO, or SO<sub>2</sub>;

R is H,

C<sub>1</sub>-C<sub>4</sub> alkyl,

phenyl or substituted phenyl,

halo,

haloalkyl,

hydroxy,

carboxy,

cyano,

C<sub>1</sub>-C<sub>4</sub> alkoxy,

C<sub>1</sub>-C<sub>4</sub> alkylthio,

C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,

C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl.

30

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nitro,  
amino,  
C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;

5 R' and R'' are independently

H,  
halo,  
C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,  
amino, or oxo, where CH-R' or CH-R''  
10 in the formula become -C=O;

R<sub>a</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl;  
R<sub>b</sub>, R<sub>c</sub> are independently, C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl,  
phenyl-C<sub>1</sub>-C<sub>4</sub> alkyl;

15

n is 0-2;

y is 1-6;

20

z is 6-20; and

wherein

25  $\begin{array}{c} R' \\ | \\ (CH)_y \end{array}$  and

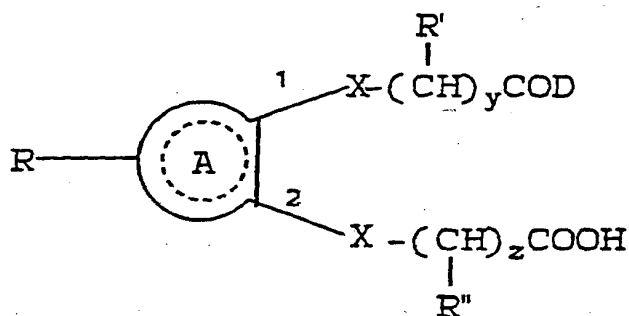
$\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$  can independently represent substituted or  
unsubstituted alkyl or alkenyl radicals  
containing at least one alkene bond;  
and pharmaceutically acceptable salts and esters  
30 thereof;

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(j) an aromatic diether or thioether compound of the structure:

5

10



wherein

A is a 1,2-disubstituted aromatic ring;

15

D is OH, NH<sub>2</sub>, NHR<sub>C</sub>, OR<sub>C</sub>;

X is O, S, SO, or SO<sub>2</sub>;

R is H,

20

C<sub>1</sub>-C<sub>4</sub> alkyl,  
phenyl or substituted phenyl,  
halo,

haloalkyl,

hydroxy,

25

carboxy,

cyano,

C<sub>1</sub>-C<sub>4</sub> alkoxy,

C<sub>1</sub>-C<sub>4</sub> alkylthio,

C<sub>1</sub>-C<sub>4</sub> alkylsulfinyl,

30

C<sub>1</sub>-C<sub>4</sub> alkylsulfonyl,

nitro,

amino,

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C<sub>1</sub>-C<sub>4</sub> mono or di-alkylamino;  
R' and R'' are independently  
H,  
halo,  
5 C<sub>1</sub>-C<sub>4</sub> alkyl or C<sub>1</sub>-C<sub>4</sub> alkoxy,  
amino, or oxo, where CH-R' or CH-R''  
in the formula become -C=O;

R<sub>a</sub> is H, C<sub>1</sub>-C<sub>4</sub> alkyl;  
10 R<sub>b</sub>, R<sub>c</sub> are independently, C<sub>1</sub>-C<sub>12</sub> alkyl, phenyl,  
phenyl-C<sub>1</sub>-C<sub>4</sub> alkyl;

n is 0-2;

15 y is 1-6;

z is 6-20; and

wherein

20  $\begin{array}{c} R' \\ | \\ (CH)_y \end{array}$  and  
 $\begin{array}{c} R'' \\ | \\ (CH)_z \end{array}$  can independently represent substituted or  
unsubstituted alkyl or alkenyl radicals  
25 containing at least one alkene bond;  
and pharmaceutically acceptable salts and esters  
thereof.

3. The method of Claim 1 wherein said  
30 aromatase inhibitor is a steroid substrate analogue

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or a non-steroid analogue which binds and inactivates aromatase or is a compound that inhibits the cytochrome P<sub>450</sub> component of the aromatase complex.

- 5                   4. The method of Claim 3 wherein the said aromatase inhibitor is selected from the group consisting of:

10           6-[(1H-imidazol-1-yl)phenyl-methyl]-1 methyl-1H-benzotriazole, 6-[(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)methyl]-1-methyl-1H-benzotriazole; 2,2-[5-(1H-1,2,4-triazol-1-ylmethyl)-1,3-phenylene]di(2-methylpropiononitrile), 2,2-[5-(imidazol-1-ylmethyl)-1,3-phenylene]-di(2-methylpropiononitrile), 2-[3-(1-hydroxy-1-methylethyl)-5-(1H-1,2,4-triazol-1-ylmethyl-phenyl)]-2-methylpropiononitrile, 2,2-[5-dideuterio (1H-1,2,4-triazol-1-yl)methyl-1,3-phenylene]di(2-trideuteriomethyl-3,3,3-(trideuterio-propiononitrile), 2,2-[5-dideuterio(1H-1,2,4-triazol-1-ylmethyl-1,3-phenylene)di(2-methyl-propiononitrile);

20           1,1-dimethyl-8-(1H-1,2,4-triazol-1-ylmethyl)-2(1H)-naphtho[2,1-b]furanone, 1,2-dihydro-1,1-dimethyl-2-oxo-8-(1H-1,2,4-triazol-1-ylmethyl)naphtho-[2,1-b]furan-7-carbonitrile, 1,2-dihydro-1,1-dimethyl-2-oxo-

25           8-(1H-1,2,4-triazol-1-ylmethyl)-naphtho[2,1-b]furan-7-carboxamide, 1,2-dihydro-1,1-dimethyl-2-oxo-8-[di(1H-1,2,4-triazol-1 yl)methyl]naphtho[2,1-b]-furan-7-carbonitrile; 2-(4-chlorobenzyl)-2-fluoro-1,3-di(1,2,4-triazol-1-yl)propane, 2-fluoro-2-(2-fluoro-4-chlorobenzyl)-1,3-di(1,2,4-triazol-1-yl)-

30           propane, 2-fluoro-2-(2-fluoro-4-trifluoromethyl-



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- benzyl)-1,3-di(1,2,4-triazol-1-yl)propane, 3-(4-chlorophenyl)-1-(1,2,4-triazol-1-yl)-2-(1,2,4-triazol-1-ylmethyl)butan-2-ol, 2-(4-chloro- $\alpha$ -fluorobenzyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol, 2-4(4-chlorobenzyl)-1,3-bis(1,2,4-triazol-1-yl)propane,
- 5 4-[2-(4-chlorophenyl)-1,3-di(1,2,4-triazol-1-ylmethyl)ethoxymethyl]-benzonitrile, 1-(4-fluorobenzyl)-2-(2-fluoro-4-trifluoromethyl-phenyl)-1,3-di(1,2,4-triazol-1-yl)propan-2-ol, 2-(4-chlorophenyl)-1-(4-fluorophenoxy)-1,3-di(1,2,4-triazol-1-yl)propan-
- 10 2-ol, 1-(4-cyanobenzyl)-2-(2,4-difluorophenyl)-1,3-di(1,2,4-triazol-1-yl)-propan-2-ol, 2-(4-chlorophenyl)-1-phenyl-1,3-di(1,2,4-triazol-1-yl)-propan-2-ol; 5-bis(4-chlorophenyl)-methylpyrimidine;
- 15  $\alpha,\alpha$ -bis(4-chlorophenyl)-2-pyrazinemethanol; N-(2,4-difluorophenyl)-N-benzyl-3-pyridinemethanamine, N-(2-chlorophenyl- $\alpha$ -(4-fluorophenyl)-3-pyridinemethanamine; 1-(10,11-dihydro-5H-dibenzo
- 20 [a,d]cyclohepten-5-yl)-1H-imidazole, 1-(9H-fluoren-9-yl)-1H-imidazole; 3-bis(4-chlorophenyl)-3-methylpyridine,  $\alpha,\alpha$ -bis(4-chlorophenyl)-3-pyridinemethanol; 5H-5-(4-cyanophenyl)-6,7-dihydro-pyrrolo-
- 25 [1,2-c]imidazole, 5H-5-(4-cyanophenyl)-6,7,8,9-tetrahydroimidazo[1,5-a]azepine; 5-[(1H-imidazol-1-yl)phenylmethyl]-2-methyl-1H-benzimidazole, 5-(3-chlorophenyl)(1H-imidazol-1-yl)-methyl]-1H-benzimidazole; (Z)- $\alpha$ -(1,2,4-triazol-1-ylmethyl-
- 30 stilbene-4,4'-dicarbonitrile, (Z)-4'-chloro- $\alpha$ -(1,2,4-triazol-1-ylmethyl)stilbene-4,4'-dicarbonitrile, (Z)-4'-chloro- $\alpha$ -(1,2,4-triazol-1-ylmethyl)stilbene-4-carbonitrile, (Z)- $\alpha$ -(1,2,4-triazol-1-

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ylmethyl)-4'-(trifluoromethyl)stilbene-4-carbonitrile,  
(E)-3-fluoro- $\alpha$ -(1,2,4-triazol-1-ylmethyl)stilbene-  
4,4'-dicarbonitrile, (Z)-4'-fluoro- $\alpha$ -(imidazol-1-  
ylmethyl)-stilbene-4-carbonitrile, (Z)-2',4'-dichloro-  
5  $\alpha$ -(imidazol-1-ylmethyl)stilbene-4-carbonitrile,  
(Z)-4'-chloro- $\alpha$ -(imidazol-1-ylmethyl)stilbene-4-  
carbonitrile, (Z)- $\alpha$ -(imidazol-1-ylmethyl)stilbene  
4,4'-dicarbonitrile, (Z)- $\alpha$ -(5-methylimidazol-1-yl-  
methyl)stilbene-4,4'-dicarbonitrile, (Z)-2-[2-  
10 (4-cyanophenyl)-3-(1,2,4-triazol-1-yl)propenyl]-  
pyridine-5-carbonitrile; (1R\*,2R\*)-6-fluoro-2-(4-  
fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-  
1-ylmethyl)naphthalene, (1R\*,2R\*)-6-fluoro-2-(4-  
fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-imidazolyl-  
15 methyl)-naphthalene, (1R\*,2R\*)-and (1R\*,2S\*)-2-(4-  
fluorophenyl)-1,2,3,4-tetrahydro-1-(1H-1,2,4-triazol-  
1-ylmethyl)naphthalene-6-carbonitrile, (1R\*,2R\*)-  
and (1R\*,2S\*)-2-(4-fluorophenyl)-1,2,3,4-tetrahydro-  
1-(1H-imidazolylmethyl)naphthalene-6-carbonitrile,  
20 (1R\*,2R\*)-and (1R\*,2S\*)-1,2,3,4-tetrahydro-1-(1H-  
1,2,4-triazol-1-ylmethyl)naphthalene-2,6-dicarbo-  
nitrile, (1R\*,2R\*)-and (1R\*,2S\*)-1,2,3,4-tetrahydro-  
1-(1H-imidazol-1-ylmethyl)naphthalene-2,6-dicarboni-  
trile, (1R\*,2S\*)-2-(4-fluorophenyl)-1,2,3,4-  
25 tetrahydro-1-(5-methyl-1H-imidazolylmethyl)naphtha-  
lene-6-carbonitrile; 8-chloro-5-(4-chlorophenyl)-5H-  
indeno[1,2-d] pyrimidine; 5-bis (4-chlorophenyl)  
methylpyrimidine; 10-(2-propynyl)-estr-4-ene-3,17-  
dione; [(4-chlorophenyl)(1H-1,2,4-triazol-1-yl)-  
30 methyl]-1-methyl-1H-benzotriazole; 1-methyl-  
androsta 1,4-dien-3,17-dione; 3-ethyl-3-(4-pyridyl)-

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piperidine-2,6-dione; 4-hydroxyandrostene-3,17-dione; 4-(5,6,7,8-tetrahydroimidazo[1,5- $\alpha$ ]-pyridin-5-yl)benzonitrile; 4-[alpha-(4-cyanophenyl)-1-(1,2,4-triazolyl)methyl]benzonitrile; 6-methylene-  
5 androsta-1,4-diene-3,17-dione, 4-amino-androstan-1,4,6-trien-3,17-dione, 4-aminoandrosta-4,6-diene-3,17-dione; 3-(1H-imidazol-1-ylmethyl)-2-methyl-1H-indole-1-propanoic acid; 5-[3-chlorophenyl](1H-imidazol-1-yl)methyl]-1H-benzimidazole; 10B-  
10 thiiranylestr-4-ene-3,17-dione, 10B-oxiranylestr-4-ene-3,17-dione; 3-ethyl-3-(4-pyridyl)piperidine-2,6-dione; 3-(4-aminophenyl)-3-ethyl-pyrrolidine-2,5-dione; 1-(7-carboxyheptyl)-imidazole; 1,1-dimethyl-8-(1H-1,2,4-tetrazol-1-yl-methyl)-2(1H)-  
15 naphtho [2,1-b]furanone (1a); 5-(p-cyanophenyl)-5.6.7.8-tetrahydroimidazo [1,5- $\alpha$ ]-pyridine hydrochloride; 1,4,6-androstatriene-3,17-dione; and bis-(p-cyanophenyl)-imidazo-1-yl-methane hemisuccinate and pharmaceutically acceptable derivatives, acid  
20 addition salts thereof.

5. The method of Claim 3 wherein said aromatase inhibitor is 4-(5,6,7,8-tetrahydroimidazo [1,5- $\alpha$ ]-pyridin-5-yl)benzonitrile  
25 hydrochloride (fadrazole).

6. The method of Claim 3 wherein said aromatase inhibitor is 1,4,6-androstatriene-3,17-dione.  
30

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7. The method of Claim 1 wherein said  $5\alpha$ -reductase inhibitor is finasteride and said aromatase inhibitor is fadrazole.

5           8. A pharmaceutical composition for the treatment of benign prostatic hyperplasia comprising therapeutically effective amounts of a  $5\alpha$ -reductase inhibitor selected from  $17\beta$ -substituted 4-azasteroids,  $17\beta$ -substituted non azasteroids,  $17\beta$ -acyl-3-carboxy-androst-3,5-dienes, benzoylamino-  
10   phenoxy butanoic acid derivatives, cinnamoylamides, fused benz(thio)amides, aromatic 1,2-diethers or thioethers, aromatic orthoacylaminophenoxy alkanoic acids, ortho-thioalkylacylaminophenoxy-alkanoic acids,  
15   or pharmaceutically acceptable ester or salts thereof, and an aromatase inhibitor in a pharmaceutically acceptable carrier therefor.

20

25

30

# INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 92/02749

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl.5      A 61 K 31/58      A 61 K 45/06      //(A 61 K 31/58 A 61 K 31:44 )		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl.5	A 61 K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	WO,A,8705216 (SCHERING AG BERLIN UND BERGKAMEN) 11 September 1987, see abstract -----	1-8
X	WO,A,9100731 (ENDORECHERCHE INC.) 24 January 1991, see abstract -----	1-8
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p><sup>10</sup> Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&amp;" document member of the same patent family</p> </div> </div>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10-08-1992	04. 09. 92,	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE		

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

US 9202749  
SA 60439

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
The members are as contained in the European Patent Office EDP file on 25/08/92.  
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A- 8705216	11-09-87	DE-A- 3607651	10-09-87
		AU-A- 7086787	28-09-87
		EP-A- 0296160	28-12-88
WO-A- 9100731	24-01-91	AU-A- 5854590	06-02-91
		EP-A- 0480950	22-04-92